Investigating associations between momentary stress and cortisol in daily life: What have we learned so far?

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ABSTRACT

Since cortisol measurement in saliva has been established, it has been used as an indicator of stress-related hypothalamic-pituitary-adrenocortical axis activity. Concurrent development of methodological frameworks such as ambulatory assessment, ecological momentary assessment, and experience sampling have provided opportunities to combine both approaches in daily life research. The current review provides a summary of basic methodological principles and recommendations, as well as abstracts of findings of studies investigating momentary associations between stress and cortisol in daily life with an emphasis on within-subject associations (i.e. average covariance in repeated momentary assessments of stress and cortisol, and individual-specific deviations from the average covariance). Methodological challenges related to stress measurement, sampling principles, and appropriate statistical modeling are discussed, followed by a description of the historical development of studies on within-subject associations between momentary daily life stress and cortisol. The review concludes with a discussion of controversial methodological characteristics of these studies regarding operationalizations of stress, compliance, timing and frequency of stress and cortisol sampling, and reporting of effect sizes. Future research in this area would benefit from automated cortisol assessment, broadening of the scope of stress response measures, use of advanced statistical models that better account for dynamics in the stress process in daily life, and attempts to replicate findings. While previous studies of momentary stress and concurrent cortisol assessments have reliably confirmed some fundamental predictions from stress theory in daily life, future studies should aim at providing progress by testing innovative research questions and utilizing new technological developments.

1. Introduction

Psychosocial stress reliably activates the hypothalamic-pituitary-adrenocortical (HPA) axis, resulting in elevations of circulating cortisol. Kirschbaum et al. (1993) demonstrated this psychoneuroendocrinological association using a specific laboratory-based motivated performance-related stressor in a social-evaluative setting including uncontrollability, the Trier Social Stress Test (TSST). A meta-analysis later demonstrated that TSST-like stressors were indeed the most potent activators of cortisol responses to stress when compared to other stressors such as cognitive tasks, noise exposure or emotion induction without uncontrollable and social-evaluative elements (Dickerson and Kemeny, 2004). This is an important contribution to various disciplines besides psychoneuroendocrinology, particularly psychosomatic medicine and health psychology, for two reasons. First, cortisol interacts with a wide variety of organ systems affecting immunological, metabolic, and cognitive functioning. Stress-related HPA axis dysregulations therefore potentially affect a wide variety of physiological processes with direct relevance for health and disease (Chrousos, 2009; McEwen, 1998). Second, stressors including motivated performance tasks and social-evaluative threat are more than artificial situations created for laboratory-based stress research. Such stressors are likely to be part of many individuals' everyday life, thereby providing a direct link between exposure to psychosocial stress and disease risk, cognition, and behavior in daily life. However, although laboratory-based stressors might resemble daily life stressors, they are not performed in the context of everyday life. It is therefore important to understand if and how stress elevates circulating cortisol in everyday life. Such studies have the potential to provide data with high ecological validity, and they present the opportunity to gain unique insights into the stress process from an idiographic perspective by modeling intraindividual processes.

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The following review will (1) describe basic methodological principles and developments that provided the basis for psychoneuroendocrinological stress research in daily life; (2) summarize research on momentary associations between stress and cortisol in daily life from its early beginnings in the 1990s to more recent times; and (3) discuss challenges and potential future developments of methods in this field.

2. Daily life research

Laboratory stress studies are carried out under highly controlled conditions implementing a variety of experimental designs. Findings from laboratory based studies have the major advantage of high internal validity. On the other hand, the laboratory setting and the highly standardized nature of laboratory stressors limit their relevance for stressors and contexts encountered in daily life and thereby restrict generalizability and external validity of results from such studies. We therefore cannot draw precise conclusions from a laboratory-based stress study's finding on stress experiences and responses of individuals in daily life contexts. While research in daily life was difficult or impossible to conduct for a long time, technological and methodological progress increasingly allowed stress research to be carried out in real life.

Daily life research methods have been systematically developed and routinely used since the 1980s. Methodological developments in this area came under different labels such as experience sampling method (Csikszentmihalyi and Larson, 1992), ecological momentary assessment (Stone and Shiffman, 1994), or ambulatory assessment (Fahrenberg and Myrtek, 1996), although daily life research methods have been implemented much earlier (for an in-depth historical review see Wilhelm et al., 2011). These methodologies share three major advantages (for a comprehensive introduction and discussion see Mehl and Conner, 2011): First, findings represent real-life experience, as they are based on data collected during participants' everyday life. Findings therefore have ecological validity as they generalize to the real world. Second, data are collected in real time (momentary assessment), which avoids bias due to retrospective assessments. Third, repeated dense sampling provides a resolution that allows individual differences in trends and dynamic temporal change to be analyzed, and simultaneous repeated assessments of different variables of interest additionally provide the opportunity to investigate associations between these variables within individuals.

The latter point represents the most important advantage of daily life research methodology besides ecological validity. Repeated assessment of momentary stress and cortisol in daily life captures a sample from a continuous characteristic for each individual. Such data allows modelling of trends (i.e. continuous functions of change over time), dynamic changes (i.e. discontinuous variability), and associations between stress and cortisol both within and between individuals. The term *within individual* (also called *within-person*, *within-subject* or *intraindividual*) refers to focusing the analysis on one specific individual, for example temporal change in cortisol or stress, or average covariance between stress and cortisol across multiple assessments for one specific person. In contrast, the term *between individual* (also called *between-person*, *between-subject*, or *interindividual*) refers to an analytic focus on aggregated characteristics of individuals, averaged across individuals. For example, a researcher might compute an aggregated measure of circulating cortisol (e.g. the mean value) and an aggregated level of stress by person, and analyze their average association across individuals. The analytic focus is of major relevance, as an analysis might lead to different conclusions on within versus between levels. For example, stress and cortisol might be positively associated within individuals (i.e. observation of high cortisol levels when an individual was under high daily life stress at that time or close before). However, in the same sample, a negative association might be observed between individuals (i.e. aggregated cortisol levels would not be systematically associated with aggregated stress levels across individuals), for example

due to HPA axis hypoactivity following chronic stress (i.e. high aggregated stress levels). Therefore, conclusions based on between-subject associations might not generalize to within-subject associations (known as the ecological fallacy). To get insight in the process underlying stress-cortisol associations as it unfolds over time, we need to sample both variables intensively and analyze within-subject associations.

The large majority of methodological progress in this area has focused on self-report data, which allowed important psychological research questions to be studied, comprising situational characteristics, emotional and behavioral responses, variability of symptoms, and more. In contrast, the essential feature of psychoneuroendocrinological stress research in daily life is its combination of assessments of psychological stress exposure and endocrine stress responses. Both variables need to be measured simultaneously or in close temporal proximity. Methodological progress in the assessment of hormones in saliva on the one hand, and refined methods to assess self-reported stressors, perceived stress, and subjective stress responses on the other hand, provided the basis for a growing number of studies on stress-related psychoneuroendocrinological processes in life as it is lived.

2.1. Assessment of cortisol in saliva

The development of salivary cortisol collection and assessment methods happened at a time when daily life research methods in other areas such as Psychology and Behavioral Medicine became more popular and refined. Traditionally, cortisol has been assessed from blood. However, taking blood is invasive, it triggers a physiological response to venipuncture, and it requires a laboratory environment including medically trained staff. The development of methods for the assessment of cortisol in saliva provided a valuable alternative to blood-based cortisol assessments. Salivary cortisol concentrations are unaffected by saliva flow rate and reflect the unbound hormone fraction, which is considered to be the physiologically active fraction of total cortisol in the body (Hellhammer et al., 1987; Kirschbaum and Hellhammer, 1989, 1994). Saliva samples for cortisol assessment can be easily collected and can be stored under conditions typically realized in daily life studies without significant changes in cortisol concentrations (Schlotz, 2011), at least across shorter time periods (some days) or when stored at −20 °C or lower (Kudielka et al., 2012). It is therefore recommended that research participants store saliva samples in their home freezer and to return them to the laboratory as soon as possible.

Today, salivary cortisol is an established and routinely used biomarker of psychological stress, mainly due to effects of various brain areas, particularly the limbic system, on the HPA axis (Ulrich-Lai and Herman, 2009). However, salivary cortisol levels do not purely reflect activity of the HPA axis at hypothalamic or pituitary levels (Hellhammer et al., 2009). The main central nervous system (CNS) effectors of the HPA axis, i.e. corticotropin releasing hormone (CRH) and arginine vasopressin (AVP), as well as adrenocorticotropic hormone (ACTH), cannot be measured in saliva. In addition, circulating salivary cortisol concentrations depend on factors such as adrenal sensitivity and corticosteroid-binding globulin (CBG) saturation, which are not related to CNS activity. Therefore, although salivary cortisol does indicate stress-relevant CNS activity to a certain degree, it cannot be expected to correlate perfectly with brain activity in relevant areas, and it cannot be used to examine HPA axis activity at the hypothalamic and pituitary level. Researchers should be aware that these are major limiting factors in psychoneuroendocrinological research on stress-cortisol associations using salivary cortisol in daily life.

While cortisol assessment in saliva stimulated laboratory-based stress research due to its more straightforward implementation compared to blood sampling, it was a prerequisite and therefore the historical point of origin of psychoneuroendocrinological stress research in daily life. Due to noninvasiveness, stability, and utility of self-conducted collection of samples by research participants, which allows

repeated assessments even with high sampling frequency, salivary cortisol assessment provided an almost ideal method for ambulatory assessment of stress-related cortisol responses in daily life studies (Schlotz, 2011).

2.2. Momentary assessment of experience

Momentary assessment has been shown to yield better self-reports of current experience than retrospective reports of past events (Robinson and Clore, 2002). For this reason, one of the essential features of daily life stress research is its focus on momentary or very recent experience (cf. Schwarz, 2011). In contrast, many psychoneuroendocrinological stress studies traditionally rely on questionnaires or interviews that ask participants to retrospectively report on past stress-related experience over some period of time, such as the Perceived Stress Scale (PSS; Cohen et al., 1983) or the Life Events and Difficulties Schedule (Brown and Harris, 1978). Although assessment methods have been developed that aim at reducing retrospective reporting bias of daily life experience (Kahneman et al., 2004), retrospective assessment methods yield aggregate measures over some time period and therefore do not provide repeated dense sampling of stress-related experience that is needed for analyzing time trends and associations of stress-related experience and cortisol concentrations within individuals. Taken together, assessments of momentary or very recent experiences have important advantages over retrospective reports, as they contain less bias and allow time trends and associations within individuals to be studied. Which stage of the stress process, and which specific facet within a process stage, is targeted by the momentary assessment can be influenced by the exact wording of items. This will be discussed further below in the section on methodological challenges.

2.3. Assessment designs

Assessments in daily life studies can be thought of as samples from experience, behavior, or physiological activity. The aim of sampling generally is to yield a representative set for the population from which the samples were drawn. Representativeness here might have different objectives, for example full everyday life, a specific sort of event, or a temporal course. Therefore, an important step in planning daily life studies is to define a sampling protocol as part of the overall study design. A sampling protocol determines scheduling of samples (timing and frequency), temporal coverage of assessments (time period to be covered), and assessment details (what is being measured), together constituting an *assessment design*. We here primarily distinguish between event-related and time-based assessment designs. The following is a short overview, more details can be found elsewhere (Schlotz, 2011; Shiffman, 2007).

2.3.1. Event-based assessment

Event-related designs focus on an event that triggers an assessment. This design could be useful to study relatively rare events, for example severe stress events in daily life. The primary focus is on the number of events, but their timing could also be investigated if time is being recorded simultaneously. The major aim is to achieve a full account of the events that occurred during the sampling period in daily life. Event-based assessments are often combined with time-based assessments to record relevant information in close proximity to the event. Event-based assessment designs rely on participants' awareness of the event happening and their willingness and capacity to report it, while compliance is hard to document. In order to be able to report an event, it has to be defined as clearly and concisely as possible, which is particularly difficult in stress research due to the wide variety of potentially relevant stressors and definitions of stress.

2.3.2. Time-based assessment

With time-based assessment designs, assessments are triggered by a sampling protocol based on time. These designs are suitable if the major aim is to generate knowledge on intensity and course of a phenomenon to be studied. Sampling intensity can be varied, with limitations due to retrospective reporting bias and restricted representativeness particularly for a temporal course if samples are triggered very infrequently (e.g. daily diaries), and high participant burden if samples are triggered very frequently (e.g. time-intensive protocols with one assessment per hour or more). What is important is that the sampling design matches the temporal characteristics of the phenomenon to be studied. Excessively long intervals between assessments might lead to strongly biased conclusions about typical trajectories. For example, daily life studies including salivary cortisol assessments need to cover the circadian rhythm of circulating cortisol (cf. Spiga et al., 2014).

Fixed-occasion designs are time-based designs where assessments are triggered at fixed time points during the day that were prespecified and are identical for all participants. This is a popular design in daily life salivary cortisol assessments and allows aggregate indicators to be computed and compared between participants. However, fixed-occasion assessments are predictable and might lead to an adjustment of individual behavior in anticipation of an assessment, for example selection of specific environments.

In *variable-occasion designs*, time points when assessments are triggered are not identical for participants and not equally spaced. In contrast, assessment times are selected randomly to achieve representative and unbiased estimates of characteristics of daily life phenomena. To avoid accidental clustering of assessments, *stratified random sampling* can be used, where the time period to be covered is divided into equal-length intervals, and one assessment is placed randomly within each interval. This can be easily achieved using smartphones for triggering assessments. Another variant of variable-occasion designs is *oversampling*, where periods of interest are being covered by increased density of assessments to achieve higher temporal resolution.

2.3.3. Combined assessment protocols

Combined assessment designs join characteristics of different assessment designs. One option is to combine different time-based designs, e.g. daily diaries plus stratified random sampling to compare anticipated with actual distress, or fixed-occasion with variable-occasion designs to investigate associations between the cortisol awakening response and stress on the upcoming day (e.g. Powell and Schlotz, 2012). Another option is to combine event-based and time-based assessment designs, for example to compare correlates of stress events with measures of the same variables when no stress event happened in a case-crossover design, or to study antecedents and consequences of stress events.

To summarize, many different assessment designs can be used for daily life research. Which assessment design should be chosen depends primarily on the phenomena to be studied, particularly their frequency and temporal characteristics, the designs' suitability for the research question, technical and financial resources, and the implied participant burden.

2.4. Compliance

Because self-administered saliva collection and repeated self-report assessments place a considerable burden on participants, missing assessments are a common problem with daily life research methods. As missingness might coincide with stress episodes, missing observations might particularly affect within-subject analyses. While it is straightforward to observe and analyze compliance with smartphone-based data, monitoring compliance with saliva collection methods is more challenging. One option is to use containers with electronic caps that record opening time. Another less expensive method is to show a random number on the smartphone that accompanies saliva collection, and ask participants to record that number on the container of the saliva collection device. Generally, motivating research participants to

adhere to instructions is fundamental for keeping compliance at a high level. This includes clear instructions, accessible communication channels, and use of incentives (cf. Adam and Kumari, 2009; Schlotz, 2011).

2.5. Covariates

It is well known that a number of time-constant and time-varying covariates affect salivary cortisol measures. Whether such factors are variables of interest or confounding variables is to be decided on the background of the research aim. Researchers should identify all relevant potential covariates in advance and assessed them in the study. They can then be controlled by using exclusion criteria for participants and/or sample; by using instructions to prevent samples being taken in close proximity; or by including assessments in the statistical model to adjust for their potential effect. The first two strategies affect representativeness and generalizability of the findings. Relevant confounders for salivary cortisol measures are medical and recreational drugs, physical and mental health, eating (meals and specific nutrients such as licorice), drinking (particularly caffeine), exercise (particularly at high intensity), smoking, age, gender, oral contraceptives, and menstrual cycle phase (cf. Adam and Kumari, 2009; Schlotz, 2011).

3. Stress and salivary cortisol in daily life

Using self-administered salivary cortisol assessments with an adequate sampling design presents the opportunity to investigate variance in circulating cortisol and covariance with self-reported stress in daily life. In the past, most studies utilized one of two different types of daily life salivary cortisol outcomes, namely (1) aggregate measures on the day-level, or (2) momentary cortisol assessments with corresponding stress assessments to investigate associations within individuals within days.

3.1. Aggregate measures of circulating cortisol on the day-level

Aggregate measures of cortisol are characterized by aggregating over repeated measures, resulting in a single indicator per individual per day (aggregation across days within individuals is also possible). The most prominent measures indicate the cortisol awakening response (CAR), total cortisol output (area under the curve, AUC), and the diurnal cortisol slope (DCS). Methodological details and standards for these indices have been reported elsewhere (Adam and Kumari, 2009; Stalder et al., 2016). It is important to note that such indices include unsystematic variance if the data come from variable-occasion designs that do not ensure representative sampling of days within individuals or time points within days within individuals. Even with sampling designs that enhance representativeness, such as stratified random sampling, aggregate measures are not strictly comparable between individuals due to variability in sampling time. Therefore, fixed-occasion designs should be used if the primary outcome variable of a study is an aggregate measure of circulating cortisol. For assessments of the CAR, consequences of inaccurate timing were shown (e.g. Smyth et al., 2016) and expert consensus guidelines on specification of measurement occasions were recently developed based on a prototypical cortisol trajectory after awakening (Stalder et al., 2016). In addition to the fixed timing of assessments, the number of samples needs to be determined carefully, as a large proportion of the total variance in such data is located within individuals, i.e. measures are highly variable between days within a given individual, including inconsistency of diurnal cycles (Hellhammer et al., 2007; Ross et al., 2014; Segerstrom et al., 2014). Therefore, an adequate assessment design should schedule more than one assessment day if an aggregate measure is the primary outcome of a cortisol daily life study.

3.1.1. Selected findings

Since the beginnings of daily life assessment using salivary cortisol, a large number of studies has investigated associations of aggregate indices with daily life stress. As the focus of these indices usually is on individual differences, studies often combined them with retrospective assessments of stress. The CAR gained particular attention since its first systematic description (Pruessner et al., 1997) as it has been shown to be observable under highly controlled sleep laboratory conditions (Wilhelm et al., 2007) and has shown a wide variety of associations with stress-related variables as well as health outcomes. These include, for example, associations of an increased CAR with chronic stress in daily life (Chida and Steptoe, 2009; Schlotz et al., 2004; Schulz et al., 1998; Steptoe et al., 2005); a lower CAR with higher levels of fatigue later that day (Adam et al., 2006); a higher CAR with reduced distress responses to daily life stress later that day (Powell and Schlotz, 2012); an absent CAR in young adults that experienced severe early life stress (Kumsta et al., 2017); and associations of the CAR with indicators of mental and physical health such as chronic fatigue, multiple sclerosis, depressive symptoms, and systemic hypertension (Nater et al., 2008; Powell et al., 2015; Pruessner et al., 2003; Wirtz et al., 2007). Aggregate indices of circulating cortisol such as the CAR, AUC, and DCS have been suggested as markers of HPA axis dysregulation, and chronic dysregulation might mediate the association between stress and negative health outcomes (Adam and Kumari, 2009; Kudielka et al., 2012). Meta-analytic review articles have indeed found supportive evidence for this role (Adam et al., 2017; Boggero et al., 2017; Chida and Steptoe, 2009; Powell et al., 2013).

3.1.2. Some limitations

Aggregate measures might seem particularly attractive indicators of circulating cortisol in daily life due to the large number of associations with a diverse range of stress-related variables and their relative simplicity in collecting and analyzing data. However, a number of caveats should be kept in mind: First, such indices include a large variance component attributable to the day level and therefore should be sampled on more than one day consecutively (Hellhammer et al., 2007; Segerstrom et al., 2014). Second, many studies have produced rather inconsistent results as evidenced by meta-analytic heterogeneity tests (cf. Boggero et al., 2017), suggesting that systematic replication studies should be conducted. Third, researchers need to monitor participants' compliance with the timing of fixed-occasion design protocols carefully, as non-compliance might introduce bias (Jacobs et al., 2005; Kudielka et al., 2003; Stalder et al., 2016). Fourth, studies on aggregate indices of circadian trends and levels often focus on between-person differences (e.g. Kumari et al., 2010; Stone et al., 2001). Although some studies investigated differences between days within individuals (e.g. Stawski et al., 2013), all of these studies disregard within-day variability by design. However, this variance component might provide valuable specific information in relation to relevant time-varying individual states as indicated by stress-related predictor variables. Finally, aggregate measures summarize circulating cortisol across time and therefore cannot be used as direct daily life equivalents of stress reactivity as assessed in laboratory studies where participants are exposed to a single stressor as a proximate cause for a subsequent cortisol response. The following section discusses approaches that utilize salivary cortisol variability within individuals *within* assessment days. Such studies provide comparatively high-resolution information on stress-cortisol associations in daily life compared to rather coarse aggregate measures.

3.2. Simultaneous assessments of stress and cortisol

Studies that reported separate variance components from repeated daily life assessments of salivary cortisol consistently found that a large percentage of variance is not accounted for by individuals or assessment day. Recalculation from reported variance components of some daily
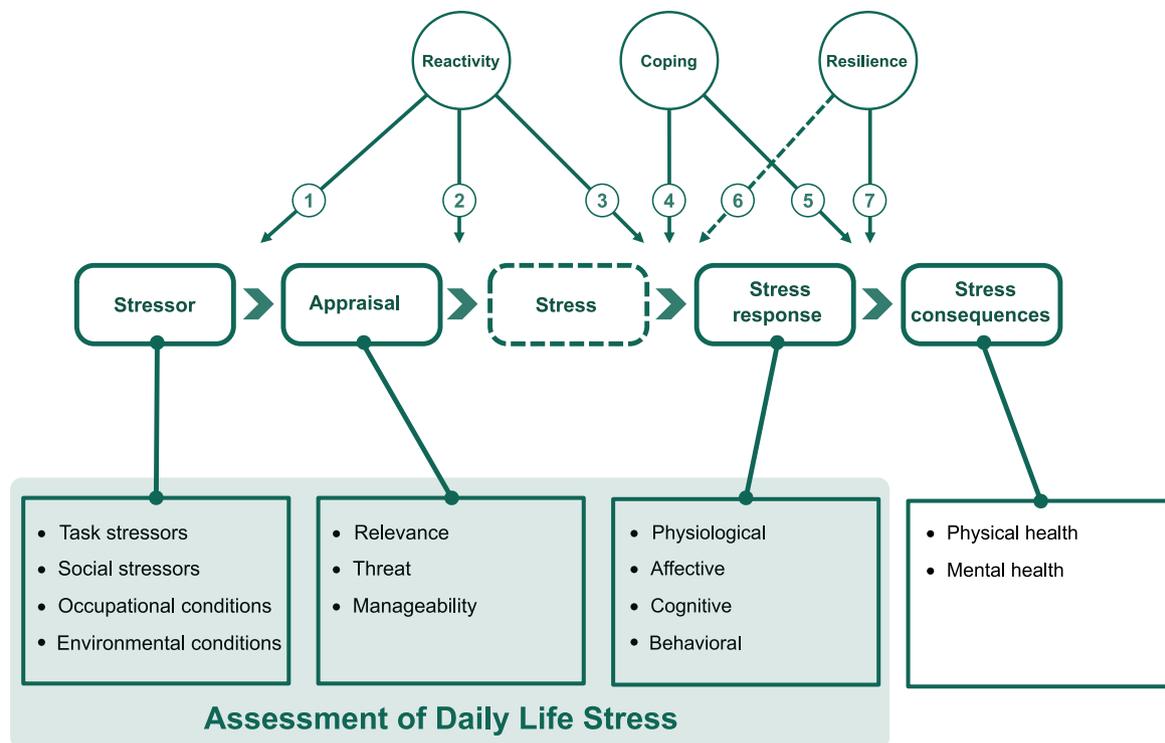
Fig. 1. A schematic stress process model that illustrates principal factors, pathways, moderators, and measurement opportunities. The central dashed box illustrates that stress itself is not directly observable, whereas antecedents, responses, moderators, and consequences are observable. The dashed arrow originating from resilience illustrates that some conceptualizations assume that resilience also affects stress response dispositions.

life studies shows that models of daily life salivary cortisol assessment adjusted for circadian trends estimated the proportion of variance *within individuals within days* at 74% (Hanson et al., 2000) 76% and 64% (two different samples in Hruschka et al., 2005), 65% (van Eck et al., 1996a), and 74% (Schlotz et al., 2006). In other words, salivary cortisol shows large variability between assessments within individuals within days, even if individual and day-specific circadian trends are accounted for.

This within-subject within-day variability might be due to a large number of factors, one of which is exposure to momentary daily life stress prior to the cortisol assessment. In the following, some basic theoretical and methodological principles will be discussed that support researchers in making design decisions when planning research studies on associations between momentary daily life stress and salivary cortisol assessments. On that basis, the subsequent section will provide a selective review of relevant research studies spanning the full time frame from very early to more recent studies.

3.2.1. A stress process model for daily life studies of stress and cortisol

Fig. 1 shows a model of the stress process that is largely in line with recent psychobiological stress theories that discern physiological stress responses in more detail (McEwen, 1998; Ursin and Eriksen, 2004). The stress process starts with an individual being exposed to a stressor, i.e. some sort of proximal cause that potentially results in stress. Based on cognitive stress theory, it is assumed that stressors lead to a state of stress only if individual appraisals result in an evaluation of the situation being relevant, a potential threat, and not manageable (Lazarus and Folkman, 1984). A stress response follows that comprises changes in four domains: physiological (e.g., HPA axis activation with cortisol increase; sympathetic nervous system activation), affective (e.g., feelings of nervousness and tense arousal), cognitive (e.g., effects on executive functions and attention), and behavioral (e.g. tendency to withdraw; detrimental health behavior). Stress responses can lead to negative stress consequences in physical and mental health, particularly (but not exclusively) via physiological responses and detrimental health

behavior (Cohen et al., 2007).

Fig. 1 also shows a number of major moderating factors that interact with this process. Stress reactivity is a disposition that underlies individual differences in the associations between stressor exposure and stress responses (Schlotz et al., 2013). Such differences in stress responses might be due to individual appraisals of stressors, as shown in path (1). Supporting this notion, a laboratory study has shown that individuals scoring high on a self-report scale assessing stress reactivity appraised the stressor as more threatening, resulting in higher cortisol responses (Schlotz et al., 2011). While moderation effects via appraisal might be relevant, they do not directly represent the common definition of stress reactivity. Traditionally, highly stress reactive individuals are thought to show stronger repsonses to states of stress. This could be due to more pronounced stress states, as shown in path (2), or to increased responses to stress states, as shown in path (3). As stress itself is not observable, these two moderating effects can be distinguished theoretically, but cannot be tested empirically. A second major moderator of the stress concept is coping, i.e. "efforts to deal with a threatening or harmful situation, either to remove the threat or to diminish the ways in which it can have an adverse impact on the person." (Carver et al., 2011, p. 222f) Coping efforts can be voluntary or automatic and might affect the intensity or composition of stress responses, as shown in path (4). More importantly, coping efforts affect consequences of stress on health as shown in path (5), primarily via behavioral (particularly health behavior) and physiological pathways (particularly via prolonged physiological responses and response system dysregulations). Finally, individuals differ in how resilient they are when exposed to stress (Southwick and Charney, 2012). Path (7) in Fig. 1 illustrates the principal concept of resilience: resilient individuals develop less detrimental health consequences despite adverse experiences such as severe or chronic stress. Less prominent is the notion that resilience might also have an effect on initial stress responses, as shown in path (6). As paths (3), (4) and (6) all affect the association between stress and stress responses, specific effects of the underlying constructs are difficult to discern empirically.

The core feature of the model in Fig. 1 is its utility in defining operationalizations for measuring daily life stress. The focal points of assessment are stressors, appraisals, and stress responses. In daily life studies that focus on effects of daily life stress on HPA axis activation, the major outcome variable will be salivary cortisol, which represents one of the major physiological stress response systems besides sympathetic nervous system activation and immunological activity. Measuring stress and cortisol repeatedly on a momentary basis and in close proximity results in multiple time-series (one per individual and day) that can be analyzed with appropriate statistical models.

A number of different hypotheses can be tested with simultaneous momentary assessments of daily life stress and salivary cortisol. The most basic, and in the majority of studies dominant hypothesis concerns the average effect of daily life stress on salivary cortisol within individuals, i.e. within-subject stress-cortisol effects. Broadly speaking, the associated parameter corresponds to cortisol responses as measured in laboratory stress studies, as it indicates the individual HPA-axis stress response capacity. However, it is an aggregate over a variety of stress episodes in daily life differing in intensity, type, and context (within and across individuals). Comparisons between subjects as well as causal inferences are therefore less straightforward than with standardized laboratory stressors. Other hypotheses might concern individual differences in average within-subject stress-cortisol associations, frequency and predictive factors of stressor exposure, effects of coping efforts, coping resources and coping styles, or predictions of later symptom occurrence by individual stress reactivity.

3.2.2. Methodological challenges

Daily life studies of momentary stress-cortisol associations present a number of specific challenges that are linked with the difficulty of integrating repeated sampling of stress and saliva into daily life, with divergent definitions of stress that complicate self-report measures of stress, and with the complexity of the resulting dataset. These challenges will be discussed in the following. The general remarks on compliance and observation of potentially confounding covariates given in Sections 2.4 and 2.5 apply here as well. To support design and analysis decisions with psychoneuroendocrinological daily life studies, some recommendations are provided in Table 1. The recommendations are specified for studies investigating within-subject associations between stress and salivary cortisol, as this is the major focus of this review. As the evidence base from relevant methodological studies is scarce or, in many cases, absent, the recommendations should be used cautiously and always on the background of the specific research question in mind.

3.2.2.1. Sampling.
When within-subject effects are of primary importance in a daily life study, a variable-occasion design can be used to achieve representativeness of the samples across the day. Stratified-random sampling with sample intervals covering most of the day should be used to ascertain that the complete within-day variability in circulating cortisol is captured, and that any average within-subject effects reflect associations across the full day. Time of day has to be recorded with every saliva sample collected to be able to adjust statistical models for circadian pattern in circulating cortisol, and samples with missing time record should be discarded before analysis. Another important issue in planning an appropriate assessment design for studying within-subject associations between momentary daily life stress and cortisol is the timing of the saliva sample relative to the assessment of stress, as stress-related salivary cortisol responses show a dynamical change that peaks approximately 10–20 min after maximum negative subjective-emotional states (Schlotz et al., 2008). It should therefore be ensured that the cortisol peak is captured either by delaying the signal for collection of the saliva sample by approximately 15 min, or by coverage of the past 30–60 min before saliva collection using a retrospective assessment period with self-report items. Keeping the retrospective period relatively short but not too short (30 min to 1 h) keeps any bias due to retrospective reporting at a minimum, while it also maximizes recording probability of relevant stress-related states. In a recent study, timing of daily stressor was retrospectively estimated by participants, and this estimation used to model the time course of emotional stress responses (Scott et al., 2017). This might be a useful alternative strategy for investigating time courses of endocrine stress responses but has not yet been used in a daily life study including cortisol assessments.

How many samples be included in an ideal assessment design to a large extend depends on the research question, technical and financial resources, and participant burden, which should be kept low as it might otherwise provoke non-compliance. A methodology study with a systematic assessment of effects of sampling frequency on within-subject stress-cortisol associations is lacking, and evidence-based recommendations therefore impossible. Past research studies have implemented a large variety of samples per day and days per participant. However, most studies have used between 5 and 10 samples per day. This number is a pragmatic compromise between representativeness of sampling and participant burden. Nevertheless, higher sampling frequencies of one per hour are possible and have been successfully implemented (e.g. Hoyt et al., 2016b; Nater et al., 2007), and more might be possible when participants are properly supported. Similarly, no study on required sample size to achieve sufficient statistical power for within-subject effects has been reported yet. For aggregate measures, five or more days of data collection are necessary to achieve acceptable reliability of CAR increase (Hellhammer et al., 2007) and DCS (Segerstrom et al., 2014). Besides reliability, design considerations should include convergence of statistical modeling algorithms for three-level models (see section 3.2.2.3.2) and participant burden.

3.2.2.2. Measuring daily life stress.
To test if changes in salivary cortisol are associated with changes in daily life stress, we need to find a suitable assessment of daily life stress. This has traditionally been done using self-reports that are triggered by a time-based variable-occasion stratified random sampling design protocol. What is being assessed critically depends on the wording of the questions asked, and on the sampling time relative to the saliva sample. Assessments may focus on stressors (stimulus-based measures), responses (response-based measures), or appraisals (appraisal-based measures) (see Kamarck et al., 2011 for a detailed review). Stimulus-based measures usually include open-ended and yes/no questions such as "has anything significant happened since the last signal?", current problems, or lists of specific events and daily hassles. Response-based measures usually include lists of negative and positive affect adjectives and Likert-type response scales. Appraisal-based measures usually include items assessing appraisals of activity (current task), social demands, and performance effectiveness on Likert-type response scales. What is important with appraisal-based measures is that the item assesses not just the occurrence of a stressor, but also its personal relevance. In addition, the effectiveness of a person's coping behavior could be assessed, e.g. does the person appraise his/her performance as adequate?

3.2.2.3. Statistical modelling.
As the statistical analysis of daily life data is complex, the following section will present a short summary of what has been identified as major issues in the statistical analysis of such data.

3.2.2.3.1. Data pre-processing.
Before data from a daily life stress study can be analyzed, a few steps of pre-processing are necessary to facilitate statistical modeling and avoid flawed analysis results. Whereas self-report data are often bounded by the response scale, salivary cortisol concentrations can yield very high values due to contamination of saliva, medication, or other factors, and should therefore be screened for outliers, which can be trimmed, winsorized or discarded (cf. Schlotz, 2011). Other data properties to be investigated include data missingness, careless responding (e.g.

Table 1

Design and analysis recommendations for studies focusing on within-subject associations between repeated simultaneous assessments of daily life stress and salivary cortisol. See text for details.

Methodological facet	Recommendation
Sampling	
Design	Stratified random sampling. Can be combined with other designs, e.g. fixed-occasion. Assessment of cortisol can be simultaneous with stress (short retrospective report possible), or delayed by approximately 15 minutes. Include assessment of potentially confounding covariates.
Participants	Should be representative for the population targeted. At least 50 participants necessary for unbiased basic statistical analysis[1] (standard linear multilevel models), but more needed if cross-level interactions are to be detected. Ideally, use a priori sample size calculation based on power analysis for mixed-effects regression models.
Days (within participants)	Number of days sampled should be representative for daily life of participant, but should also account for burden to participants, statistical power, and convergence of statistical algorithm. Studies on aggregate cortisol measures suggest at least 5 assessment days. Increase number of days if research question is focused on within-subject, between-day variability (e.g. weekend vs. weekdays).
Assessments (within days within participants)	Sampling frequency should be sufficient to represent the within-day dynamics of salivary cortisol variability, representative for daily life of participant, but should also account for burden to participants, statistical power, and convergence of statistical algorithm. Most studies successfully implemented 5 to 10 assessments per day. Exact timing of assessment needs to be recorded. Saliva samples to be stored in freezer by participant.
Compliance	
Enhancing	Provide clear instructions on how and when to provide samples. Support compliance by practicing one assessment in lab, use incentives for completed assessments, provide online/phone support, allow (moderate) postponing of assessment.
Reporting	Record compliance using electronic monitoring or ask participant to record random number presented by smartphone on salivette container. Report compliance rate separately for self-report and saliva samples.
Statistical analysis	
Model type	Multilevel/ mixed-effects regression modeling.
Data preprocessing	Check for outliers, data missingness, careless responding, time record issues, and time intervals between measures.
Steps	Separate within- from between-subject variance by centering predictors. Detrend cortisol time series. Include relevant covariates first, and then include predictors of interest.
Checks	Check model assumptions (linearity; normality of residuals at all levels). Do sensitivity analysis to check for influence of outliers, observations of unclear data quality, and data missingness.

[1]Based on a simulation study with two-level models (Maas and Hox, 2005); note that generalizability to three-level models is unclear, and larger samples might be needed to detect small effects.

reports completed too quickly), time record issues, and actual time intervals between assessments. In addition, the distribution of salivary cortisol collected across the day usually is skewed. Often, transformation (cf. Miller and Plessow, 2012) is useful to linearize the circadian trajectory and to meet the assumptions of linear statistical models. Finally, predictor variables should be within-person centered to avoid confounding of between- and within-subject effects (cf. Wang and Maxwell, 2015).

3.2.2.3.2. Multilevel/ mixed-effects-regression models. Momentary assessments from a variable-occasion random sampling protocol yield complex multilevel longitudinal data where observations are nested within days, and days are nested within individuals. The statistical method of choice to analyze such data is multilevel/mixed-effects regression modelling (e.g. Hedeker and Gibbons, 2006), which can be applied using a variety of statistical software packages (e.g. West et al., 2014). These methods have the major advantage of being able to model nested effects, accounting for the complex data structure. Major benefits are uninflated error rates, estimation of average within-subject associations as well as individual deviations from average effects, and high flexibility in testing a variety of hypotheses by appropriate model specifications. In addition, such models present high flexibility in modelling of heteroscedasticity and autocorrelation in the data (cf. Liu et al., 2012), and full information maximum likelihood estimation under certain assumptions adequately accounts for missing values in the data matrix.

A first step of model building should detrend the time series on the day-level to remove the circadian trend of cortisol measures. This can be achieved by including assessment time as a predictor in the model (cf. Wang and Maxwell, 2015), both as a fixed and random effect (accounting for individual variability). A linear component might be sufficient if cortisol data were transformed, but quadratic and cubic components can be added to the model as needed. We are modelling transformed salivary cortisol measures (indicated by *TCort*) by a linear time predictor (indicated by *CTime*, where *C* indicates that the variable should be centered at a meaningful value) for observation *t* (level-1

unit) nested within day *d* (level-2 unit) nested within individual *i* (level-3 unit) with $t = 1...N_{di}$, $d = 1...N_i$, and $i = 1...I$. The mixed-effects regression representation of this model is given as:

$$(TCort_{tdi}) = \gamma_{000} + \gamma_{100}(CTime_{tdi}) + v_{00i} + u_{0di} + v_{10i}(CTime_{tdi})$$
$$+ u_{1di}(CTime_{tdi}) + e_{tdi} \quad (1)$$

Here, γ indicates fixed effects, namely the intercept parameter γ_{000} indicates the transformed cortisol grand mean at $CTime = 0$, and the slope parameter γ_{100} represents the average change in *TCort* when *CTime* increases by one unit (e.g. one hour, if *CTime* was on an hourly unit scale). The random effects v and u represent individual- and day-specific deviations: v_{00i} represents the deviation of an individual's intercept, i.e. mean *TCort* level, across days from the average intercept across all individuals and days, and u_{0di} is the intercept deviation on a specific day within a given individual. Similarly, v_{10i} represents the individual-specific slope deviation (across days) from the average slope parameter (indicating change in *TCort* by *CTime*), and u_{1di} the within-individual day-specific deviation from the individual's average slope across days. Finally, e_{tdi} represents the residual not accounted for by model parameters. This is the deviation of observed cortisol from the cortisol value predicted by the model accounting for individual and day-within-individual trends, i.e. the circadian cortisol rhythm. An important model assumption that should be checked when applying such a model is that all residuals (here vs, us, and e) are assumed to be multivariate normally distributed with a mean of zero and specific variance and covariances.

This basic model can be expanded flexibly by including predictors that vary at the individual level (e.g. personality traits, sex, use of oral contraceptives), at the day level (e.g. sleep quality, anticipation of stress on the upcoming day), and at the measurement occasion level (e.g. momentary affect, recent exercise or coffee intake). As salivary cortisol measures are susceptible to effects of various variables that might confound the effect of interest, potentially influential covariates should be included and retained in subsequent models if statistically relevant.

The model including P level-1 covariates (indicated by Q) is given by:

$$
\begin{aligned}
(TCort_{tdi}) = {} & \gamma_{000} + \gamma_{100}(CTime_{tdi}) + \sum_{p=1}^{P} \gamma_{200p}(Q_{ptdi}) + v_{00i} + u_{0di} \\
& + v_{10i}(CTime_{tdi}) \\
& + \sum_{p=1}^{P} v_{20ip}(Q_{ptdi}) + u_{1di}(CTime_{tdi}) + \sum_{p=1}^{P} u_{3dip}(Q_{ptdi}) + e_{tdi}
\end{aligned}
\tag{2}
$$

Here, γ_{200p} represents the average effect of covariate Q_p on cortisol, the random effect parameters indicate equivalent effects as described before, and the same assumptions apply. Note that including many random effects and covariances between random effects might lead to convergence problems, so they should be retained in the model parsimoniously. Similarly, covariates measured at the day-level (e.g. sleep quality) or the level of the individual (e.g. sex), as well as their interaction with time, can be included in the model. Note that indicators of measurement occasion and day, respectively, as well as random effects of that level have to be omitted accordingly.

The residual not accounted for by circadian trend modelling and potentially confounding covariates is the target for prediction by time-varying predictors of interest, here corresponding momentary assessments of stress. A model for prediction of transformed cortisol by momentary stress (indicated by *CStress*, where *C* indicates that it should be centered at the day- and individual-specific mean, respectively) can be represented by:

$$
\begin{aligned}
(TCort_{tdi}) = {} & \gamma_{000} + \gamma_{100}(CTime_{tdi}) + \sum_{p=1}^{P} \gamma_{200p}(Q_{ptdi}) + \gamma_{300}(CStress_{tdi}) \\
& + v_{00i} + u_{0di} \\
& + v_{10i}(CTime_{tdi}) + \sum_{p=1}^{P} v_{20ip}(Q_{ptdi}) + v_{30i}(CStress_{tdi}) \\
& + u_{1di}(CTime_{tdi}) + \sum_{p=1}^{P} u_{3dip}(Q_{ptdi}) + u_{2di}(CStress_{tdi}) + e_{tdi}
\end{aligned}
\tag{3}
$$

Here, γ_{300} represents the average effect of stress on cortisol adjusted for the diurnal trend and covariates included, i.e. this parameter represents the average change in cortisol by a 1-unit increase in stress conditional on diurnal trend and covariates. Similar to the random effects described for formula (1), v_{30i} and u_{3di} indicate individual- and day-within-individual-specific deviations from the average stress-cortisol association, and the same assumptions apply. Of course, predictors of interest at the day-level (e.g. anticipation of experiences for the upcoming day) or level of the individual (e.g. personality) can be included in the model (omitting indicators and random effects accordingly). Such variables will predict variance at their respective level, and they can be used for model extensions such as including cross-level interactions (e.g. personality x stress).

Taken together, mixed-effect regression models provide a flexible statistical framework for modelling salivary cortisol in daily life in general, and within-subject associations specifically. Researchers should detrend the time series in a first step, then add relevant potentially confounding covariates, and finally include within-subject and between-subject predictors (and interactions) in the model.

3.2.3. Empirical evidence for within-subject stress-cortisol associations in daily life

The variety of methodological challenges described above might have contributed to a rather small number of daily life studies on within-subject associations of stress and cortisol being published since salivary cortisol measurement has been established.

3.2.3.1. Studies with ordinary population samples. Two initial publications (Ockenfels et al., 1995; van Eck and Nicolson, 1994) presented data from studies that had collected momentary self-reported stress and salivary cortisol measures, but both used suboptimal statistical models and did not find any within-subject associations. Both datasets were later reanalyzed using mixed-effects regression modeling and found significant within-subject effects. The reanalysis of the Ockenfels et al. data (Smyth et al., 1998) found that reporting a

current or anticipated stressful event was significantly associated with momentary salivary cortisol, and stressor appraisal also had a significant within-subject effect. In addition, positive and negative affect were significantly associated with cortisol, and within-subject mediation of the stressor-cortisol association was supported by the findings. Similarly, reanalysis of the van Eck and Nicolson data found that reporting stressful event occurrence since the last signal, as well as ongoing events, had a significant within-subject effect on momentary salivary cortisol; moreover, high scores on momentary negative affect and agitation were related to momentary cortisol and were suggested to mediate the within-subject stressor-cortisol association (van Eck et al., 1996a). As this participant sample also completed a laboratory-based stress task, it presented the opportunity to test if cortisol responses to the laboratory stress task were associated with cortisol responses to daily life stress. Although some associations were found between laboratory and daily life cortisol, stress responses in the laboratory and average responses in daily life were not significantly associated (van Eck et al., 1996b). These studies set the stage for future studies on within-subject stress-cortisol associations in daily life that tested similar as well as new hypotheses.

Hanson et al. (2000) investigated if specific momentary occupational stress, effort-reward imbalance, was associated with salivary cortisol within individuals. While this effect was not significant, momentary negative affect was positively associated with salivary cortisol, confirming earlier findings. A study on appraisal-based task-related stress measures reported positive within-subject associations of pressure to perform on momentary salivary cortisol, and demonstrated that individual variability in this effect was moderated by trait anxiety (Schlotz et al., 2006). Adam (2006) reported positive within-subject associations of momentary measures of subjective-emotional stress with momentary cortisol within adolescents. Whereas sample sizes in these previous studies were relatively small (up to 100), a study published in 2007 implemented a rather large-scale assessment design with 10 assessments per day, 5 days per individual, and 556 (all female) participants (Jacobs et al., 2007). Results of this study confirmed those from earlier studies by demonstrating a within-subject effect of momentary activity-related and social daily life stress and momentary negative affect on salivary cortisol measures, as well as mediation of the stress-cortisol association by negative affect. Results of two more recent studies largely confirmed these findings: Harter and Stone (2012) found a positive within-subject association of momentary stress appraisal measures with increased momentary cortisol, and a negative association of momentary 'interest' with momentary cortisol. Giesbrecht et al., 2012 found a within-subject effect of momentary negative mood on cortisol in pregnant women. However, another study recently did not find a significant within-subject effect of occurrence of daily life stressors (daily hassles) on momentary cortisol (Smyth et al., 2017).

Two studies investigated solitude/loneliness as a specific potential social stressor. Momentary self-reports of being alone, as well as momentary negative affect, were reported to be associated with increased momentary cortisol (Matias et al., 2011). In contrast, the other study did not find this effect using self-reports of lonely/sad, and the effect of momentary subjective-emotional stress on cortisol was also not statistically significant (Doane and Adam, 2010). With a focus on the role of coping in the daily life stress process, two recent studies found some evidence for the relevance of momentary coping behavior for within-subject stress-cortisol associations in daily life in subgroups of individuals with low trait engagement coping (Sladek et al., 2016) and internalizing disorders (Gilbert et al., 2017).

In conclusion, the number of daily life studies on within-subject stress-cortisol associations is steadily increasing. While the first studies mostly successfully tested very basic hypotheses on within-subject associations of stress with cortisol, constructs included became more diverse in recent studies. Future studies should continue to test additional constructs and innovative hypotheses.

3.2.3.2. Studies with clinical samples. Studies applying simultaneous ambulatory momentary stress and salivary cortisol assessments present the opportunity to investigate if clinical groups might show specific within-subject stress-cortisol associations in their daily life, which would add to any such evidence from laboratory studies and has potentially high relevance due to the ecological validity of such findings. An initial study in participants with major depressive disorder (Peeters et al., 2003) showed that the occurrence of stressful events was, as expected, positively associated with salivary cortisol in healthy participants, whereas no significant association was found in participants with depression (the contrast between participant groups was significant). In contrast, momentary negative affect was similarly associated with higher momentary cortisol in both groups. Reduced within-subject effects of daily life stressors on cortisol have also been found in bipolar patients with many previous episodes (Havermans et al., 2011). In addition, studies on patients diagnosed with psychotic disorder, first degree relatives, and healthy control participants showed significantly different within-subject associations of momentary stressors with cortisol in these groups (Collip et al., 2011; Vaessen et al., 2018). Interestingly, the effect of daily life stress on cortisol was stronger in relatives that had a comparatively small hippocampal volume (Collip et al., 2013).

In conclusion, only few studies have tested within-subject stress-cortisol associations in daily life using clinical samples. However, these studies demonstrate that this sort of research is feasible and has the potential to yield innovative and relevant insights into daily life stress processes in individuals with clinical disorders.

3.3. Discussion

With the establishment of salivary cortisol as a marker of HPA axis activity and the progress in methodological expertise from the areas of ambulatory assessment, ecological momentary assessment, and experience sampling, researchers increasingly adopted the opportunity to conduct studies on associations between stress and circulating salivary cortisol in daily life. While aggregate measures such as the CAR, AUC or DCS were adopted very quickly, and studies are still appearing in rather large numbers, studies on associations between momentary stress and salivary cortisol within individuals had a slower start. This is very likely due to the relatively high complexity of organizing such studies, the costs involved, and the challenges presented by operationalizing stress, defining an appropriate assessment design and adequately modeling the resulting data. However, the number of studies is growing, probably because more researchers see the opportunities presented and are willing to overcome the challenges involved. Studies of within-subject stress-cortisol associations have opted for a variety of different ways to deal with typical methodological challenges.

First, a large variety of operationalizations of stress has been implemented, including a range of stimulus based stressor measures from daily hassles to post-hoc coding of open-ended stress event items, stress appraisal measures of different sorts, and response-based measures primarily indicating subjective-emotional responses to stress. The studies review above suggest that all operationalizations have utility, depending on research questions and context. However, comparative studies investigating the relative contribution of different types of stress assessments are lacking. In addition, to clarify an item's validity, it would be useful to examine the response process from the perspective of the individual participant during answering a question on stress exposure or experience, as has been recently done with related daily life assessments (Junghaenel et al., 2017). Daily life stressor measures should ideally cover a large range of stressors, as they occur rather infrequently in everyday life. For example, occurrence of performance pressure has been clearly affirmed at only 11%, task failure at only 4% (Schlotz et al., 2006), and a current problem at 27% of assessments (using an open item; Smyth et al., 1998). Frequency clearly depends on the exact wording of the item, and stressors differ in their impact. While

daily hassles are more frequent than more severe stressors, they likely have less impact on stress responses. Therefore, researchers should carefully select item wording while keeping the research question in the focus.

Second, self-implemented collection of saliva samples is usually done using collection devices that participants need to carry with them in daily life, which is a burden to participants and might reduce the willingness to take part, or limit compliance with the research protocol. Although compliance rates reported were appropriate (maintained by incentives and appropriate support for participants), and post-study surveys usually reveal only little issues, compliance rates differ between studies. Generally, daily life cortisol studies would profit from less time-consuming and laborious assessments of cortisol.

Third, the exact timing of saliva collection relative to its corresponding assessment of stress (traditionally via self-report) is difficult to choose, as peaks in cortisol occur approximately 15 min after peaks in subjective stress (Schlotz et al., 2008). However, the review of studies here showed that very different protocols actually were equally effective, including a 25 min lagged saliva collection (Smyth et al., 1998), retrospective self-report items covering the past hour (Schlotz et al., 2006), and concurrent stress assessments (Jacobs et al., 2007). Nevertheless, it would be useful to expand our knowledge on maximum stress-cortisol cross-correlations in daily life.

The stress process model for daily life research shown in Fig. 1 seems to be useful, as it is supported by findings showing that more proximate negative affective states mediate within-subject associations between stressor- or appraisal-based measures and momentary cortisol. While the mediation models tested are based on a valid rationale, more adequate statistical models should be used if random effects are included (Bauer et al., 2006), and tests of moderated mediation might provide very interesting insights into individual-specific paths in the stress process.

Another issue with existing studies is related to the fact that no study reported size of effects in terms of explained variance. While it is notoriously complex to define effect size measures for multilevel models, solutions have been proposed (Rights and Sterba, 2018) and should be used. It might well turn out that the proportion of salivary cortisol variance that can be explained by daily life stress measures is very limited (cf. Hellhammer et al., 2009), but that would be useful information as well. Similarly, norm values would help to facilitate comparison of results from different studies. While this is particularly difficult to achieve for within-subject stress-cortisol associations, an initial attempt describing unstimulated cortisol concentrations in daily life (Miller et al., 2016) might serve as a template.

While no evidence for optimal sampling frequency for salivary cortisol in daily life exists, most studies have used between 5 and 10 assessments per day. Although this seems to work well for modelling circadian trends and find conditional effects of daily life stress, high frequency changes in circulating cortisol might not be detected. It has been suggested that cortisol release follows an ultradian, pulsatile pattern (Lightman et al., 2008) that might be important for normal emotional and cognitive functioning (Kalafatakis et al., 2018). Investigation of such effects in daily life requires higher sampling frequencies and application of appropriate pulse detection criteria (cf. Miller et al., 2013). The fact that the AUC is sensitive to low-frequency sampling (Hoyt et al., 2016a) suggests that important cortisol peaks are neglected. This would also affect within-subject stress-cortisol associations and suggests that rather more than less saliva samples should be scheduled in standard assessment designs. Methodological studies on required sample sizes (assessments per day, and assessment days per participant) are much needed to facilitate evidence-based design decisions when planning studies focusing on stress-cortisol associations within-subjects.

Although this review is focused on salivary cortisol, it is important to mention that a variety of alternative biomarkers such as dehydroepiandrosteron (DHEA; sulfate, DHEA-S), testosterone, estradiol,

alpha-amylase, immunoglobulin A (sIgA) could additionally be measured from the same saliva samples. Although this broadens the opportunities for psychoneuroendocrine daily life studies, researchers need to consider specific methodological requirements for some of these measures. More in-depth discussions on the variety of salivary biomarkers can be found elsewhere (Granger and Johnson, 2013; Schlotz, 2011).

4. Conclusions and future directions

Daily life studies investigating associations of stress and cortisol have a number of unique advantages. First, they provide representative samples of stressors and stress responses for individual everyday life; second, they allow individual differences in stress reactivity to be investigated; third, they offer the opportunity to examine relevant contextual variables such as social or occupational factors; fourth, they limit retrospective reporting bias; and finally they facilitate the ecological validity of findings. Existing studies reviewed here demonstrate the utility of this methodology. However, these studies have only tested some of most straightforward hypotheses and have used limited technology. Future developments might open up this research area in several different ways.

As self-administered saliva collection is burdensome to participants, new technologies for ambulatory assessment would be a major step forward. While initial developments have been presented for automated continuous measures (Bhake et al., 2013) and technologies that enable point-of-care measures (Kaushik et al., 2014), more research and development is needed before they can be routinely used in daily life studies.

Daily life studies in the past have mainly focused on salivary cortisol and subjective-emotional stress responses. Future studies should broaden the scope of response measures by including other psychophysiological measures (e.g. Looser et al., 2010) and other response domains. Future studies should explore the utility of methods such as smartphone-based cognitive tests (Schuster et al., 2015), automated emotion recognition via facial expressions (Du et al., 2014), and smartphone sensing methods to measure behavior objectively (Harari et al., 2017).

In addition, statistical models that go beyond basic mixed-effects regression modeling should be used in future daily life stress-cortisol studies. Varieties of more complex dynamic models have been proposed for daily life research (Walls and Schafer, 2006). For example, investigating autoregressive effects more deeply has been shown to reveal differences between depressed participants and healthy controls (Peeters et al., 2004). Finally, continuous time modelling (e.g. Voelkle and Oud, 2013) might provide particularly interesting new insights on cross-correlations between repeated subjective-emotional states and cortisol measures that have been demonstrated in past research (Het et al., 2012; Hoyt et al., 2016b; Schlotz et al., 2008).

Although daily life studies on within-subject associations of stress and cortisol have produced rather consistent findings of basic processes, studies on aggregate measures are more heterogeneous. Therefore, systematic replication studies should be encouraged and supported by reporting guidelines (Stone and Shiffman, 2002). To facilitate replication, daily life researchers could consensually develop new structured, comprehensive, and binding standards for reporting of daily life studies that should also include cortisol assessments.

Finally, daily life stress/cortisol measures might be utilized for clinical assessments. A prerequisite here would be future research on development of norm values and cut-off criteria indicating individual health risk and resilience. Daily life research methodology presents a number of unique opportunities for clinical research and assessment (Trull and Ebner-Priemer, 2013). In an initial conceptual publication, Hellhammer et al. (2012) have suggested salivary cortisol assessment in daily life as a useful diagnostic tool in clinical assessment.

Taken together, we have learned from previous research on

associations between stress and cortisol in daily life that studies are feasible, also in clinical groups, and that appropriately designed studies produce results that are largely in line with theoretical expectations. Associations between momentary stress and cortisol within individuals were mostly confirmed across studies and are particularly interesting as they represent an ecologically valid correspondent to laboratory stress studies.

However, we still need to learn more about stress-cortisol associations in daily life, particularly their dynamics and underlying factors; effect sizes and replicability; optimal sampling frequency and boundary conditions for maximum participant compliance and convenience; their potential prognostic value for mental and physical health; associations of momentary subjective-emotional and cortisol stress responses with indicators of stress responses in other domains; and finally biological, psychological, and social mechanisms underlying increased stress reactivity in daily life. Future technological and methodological research and development will provide innovative tools for studies that will provide valuable new insights into stress-related psychoneuroendocrine processes in daily life.

Declarations of interest

None.

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