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Stability of diurnal cortisol measures across days, weeks, and years during middle childhood and early adolescence: Exploring the role of age, pubertal development, and sex

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ABSTRACT

Effective regulation of the hypothalamic-pituitary-adrenal axis (HPA-axis) has been linked to numerous health outcomes. Within-person variation in diurnal measures of HPA-axis regulation assessed over days, months, and years can range between 50–73% of total variation. In this study of 59 youth (ages 8–13), we quantified the stability of the cortisol awakening response (CAR), the diurnal slope, and tonic cortisol concentrations at waking and bedtime across 8 days (2 sets of 4 consecutive days separated by 3 weeks), 3 weeks, and 3 years. We then compared the stability of these indices across three key developmental factors: age, pubertal status, and sex. Youth provided 4 saliva samples per day (waking, 30 min post-waking, before dinner, and before bedtime) for 4 consecutive days during the 3rd week of an ongoing 8-week daily diary study. Youth repeated this same sampling procedure 3 weeks and 3 years later. Using multi-level modeling, we computed the amount of variance in diurnal HPA-axis regulation that was accounted for by nesting an individual's diurnal cortisol indices within days, weeks, or years. Across days, diurnal slope was the most stable index, whereas waking cortisol and CAR were the least stable. All indices except bedtime cortisol were similarly stable when measured across weeks, and all indices were uniformly stable when measured across 3 years. Boys, younger participants, and youth earlier in their pubertal development at study enrollment exhibited greater HPA-axis stability overall compared with females and older, more physically mature participants. We conclude that important within- and between-subjects questions can be answered about health and human development by studying HPA-axis regulation, and selection of the index of interest should be determined in part by its psychometric characteristics. To this end, we propose a decision tree to guide study design for research in pediatric samples by longitudinal timeframe and sample characteristics.

1. Introduction

Salivary indices of diurnal HPA-axis regulation have been used for the past two decades to better understand human development (Gunnar and Quevedo, 2007; Gunnar and Donzella, 2002) and the neurobiological underpinnings of health and disease (McEwen, 2013; Pariante and Lightman, 2008). More recently, HPA-axis indices have emerged as a useful indicator of intervention effectiveness in targeted high-risk groups (Slopen et al., 2014). These HPA-axis indices are most commonly measured through salivary cortisol, which is cost effective and amenable to collection in almost any setting (Saxbe, 2008). Yet, up to 50% of variability in diurnal indices of HPA-axis functioning can be attributed to day-to-day changes in mood, sleep, diet, sampling error, and other factors (Ross et al., 2014; Segerstrom et al., 2014). Some indices are more stable over time than others (e.g., diurnal slope appears to be more stable than CAR) (Doane et al., 2015; Shirtcliff et al., 2012) and are therefore more appropriate for between-subjects hypothesis testing while other indices may be better suited to within-

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subjects hypothesis testing. The purpose of this study was to determine the stability of these different indices of diurnal cortisol regulation across days, weeks, and years in a well-characterized, longitudinal sample of youth, and to examine the roles of age, pubertal status, and sex in the stability of these indices. The results have the potential to inform study design decisions for investigators interested in optimizing for within- or between-subject variability when integrating salivary measures of diurnal HPA-axis regulation in longitudinal studies of varying lengths of time.

Much research using diurnal HPA-axis measures to date has been conducted in the context of understanding the links between health and disease. To this end, investigators have focused largely on determining how well-established health-relevant risk factors are associated with differences in trait-like indices of HPA-axis regulation (Bower et al., 2005; Cohen et al., 2006; Doane et al., 2015, 2013; Kuhlman et al., 2015). Another line of research has pursued insight into within-person sensitivity to short-term changes in life stress, mood, and social interactions (Adam et al., 2006; Almeida et al., 2009; Bai et al., 2017; Kuhlman et al., 2018, 2016, 2016). Further, the importance of investigating the effects of psychosocial interventions on biological processes is promising (Rauch et al., 2017; Slopen et al., 2014) and growing (Zalta and Shankman, 2016). Integrating diurnal measures of HPA-axis functioning into intervention studies will necessitate sensitive measures of both within-subject and between-group differences. Thus, trait-like and state-like indices of diurnal HPA-axis functioning have value in our pursuit of the social, environmental, and psychological factors that influence health and development. Yet, the vast majority of studies operationalize diurnal HPA-axis functioning in the same way, regardless of the within- or between-subject nature of the research questions. This is, in part, due to lack of clarity about the appropriateness of different HPA-axis indices for capturing within- and between-subject effects.

There are several ways to measure functioning of the HPA-axis that offer unique insight into the daily regulation of the HPA-axis, with the vast majority of studies today measuring cortisol assayed from saliva. Cortisol concentrations are relatively high in the morning, exhibit a dramatic increase within one hour of waking, and decline throughout the day. While some studies have identified cortisol concentrations at specific times of day that may be relevant to health (Goodyer et al., 2000; Kirschbaum et al., 1990), indices computed from multiple samples in a day, across multiple days, are currently the standard in the field (Adam and Kumari, 2009). The most common of these computed indices are cortisol awakening response (CAR) and the diurnal slope. CAR is the magnitude of cortisol increase that occurs immediately upon waking, is thought to index adrenal sensitivity to adrenocorticotropic hormone (Clow et al., 2010), and appears to be sensitive to short-term changes in the social environment (Adam et al., 2006; Chida and Steptoe, 2009). Importantly, CAR has emerged as a reliable prospective predictor of depression (Adam et al., 2010; Kuhlman et al., 2017b; Vrshek-Schallhorn et al., 2013). The diurnal slope is used to capture the circadian down-regulation of cortisol from waking to bedtime. Individuals with different health conditions and poor prognoses also tend to lack a steady decline in cortisol throughout the day (Bower et al., 2005; Schrepf et al., 2015; Sephton et al., 2013, 2000). There are two common approaches to calculating diurnal slope. One approach regresses sampling time on all available cortisol measurements that day to yield an estimated slope of change across the day (See Bower et al., 2005; DeSantis et al., 2007; Doane et al., 2013; Ross et al., 2014 for examples using this method). However, daily experiences such as stress, exercise, and diet can contribute to variability in slopes that are distinct from the circadian rhythm. For this reason, another common approach to computing the diurnal slope is to subtract the cortisol concentration at waking from the cortisol concentration at bedtime, and divide that value by the number of hours between waking and bedtime (Hoyt et al., 2016; Kuhlman et al., 2017b, 2016). Each of these indices and their computation likely represent different underlying neurobiological processes, and therefore may be differentially sensitive to changes in an individual's life over time. The present study sought to determine the stability of different diurnal HPA-axis indices in order to provide clarity on which index can be used to optimally address within-subjects versus between-subjects research questions in pediatric samples while also balancing scientific ambitions with participant burden.

Several seminal papers have considered aspects of this issue, although they have largely focused on identifying the best trait measure of individual differences in diurnal HPA-axis regulation. Cortisol concentrations at waking and at 30 min after waking appear to be useful as trait-like indicators of individual differences in diurnal HPA-axis regulation (Doane et al., 2015; Kirschbaum et al., 1990). In a seminal study, 357 youth were followed from age 9 to age 15 to determine a trait measure of diurnal cortisol regulation that models all samples across the day simultaneously (Shirtcliff et al., 2012). The investigators determined that while 13% of the variation in cortisol levels was due to trait-like factors, the circadian rhythm of cortisol was 72% trait-like across the transition from childhood to adolescence (Shirtcliff et al., 2012). For comparison, in personality research, "trait-like" self-report measures demonstrate stability coefficients of .41 and higher, with stability lower in childhood than any other developmental phase and stability higher across shorter timeframes (e.g., days and weeks versus years) (Caspi et al., 2005; Roberts and DelVecchio, 2000). Additionally, Ross et al. (2014) compared the stability of multiple diurnal HPA-axis indices (CAR, total cortisol across the day (AUC), and diurnal slope) using data from three samples that ranged from childhood to middle adulthood with cortisol assessed multiple times for up to two years. They concluded that diurnal cortisol indices have some trait-like properties, but that diurnal HPA-axis indices are better indicators of short-term (day-to-day), rather than long-term (months and years), stress and health processes (Ross et al., 2014).

Shirtcliff et al. (2012) also showed that gender and development played important roles in the maturation of the HPA-axis (Shirtcliff et al., 2012). Specifically, females had higher cortisol and steeper circadian rhythms than males, and adolescents had lower cortisol concentrations in the morning and higher concentrations in the evening compared to concentrations when they were 9 years old (Shirtcliff et al., 2012). Importantly, these developmental changes were attributable to age rather than puberty (Shirtcliff et al., 2012).

Taken together, the studies cited here indicate that there are HPA-axis indices that can be used as trait measures of underlying neurobiological development and health over multiple years (e.g., circadian rhythm or diurnal slope) while others are more state-like (e.g., CAR) and better suited to assessing an individual's response to short-term changes in the environment across days and weeks. Yet, to our knowledge, no guidelines exist for selecting diurnal indices of HPA-axis regulation based on differences in measure stability. This paper approaches the question of stability by assessing the extent to which within-person variance contributes to total variability in waking cortisol, CAR, the diurnal slope, and bedtime cortisol in a sample of youth across three different timeframes: days, weeks, and years. Further, we will characterize how the different stability estimates vary according to three developmental factors: age, pubertal status, and sex.

2. Method

2.1. Participants

Participants in the present study were part of a study of the daily lives of children (8–13 years) and their families across an initial 8 week daily diary assessment period and a 3 year follow-up assessment (Reynolds et al., 2015; Robles et al., 2013). Participants were recruited from public schools, pediatric clinics, community centers, newspaper advertisements, and direct mailings between 2009 and 2012. A total of 59 youth enrolled in the study (47 target children and 12 siblings). Families were eligible for the study if they were currently living in two-