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Intra-individual cortisol variability and low-grade inflammation over 10 years in older adults

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ABSTRACT

Objective: This study examined the associations between intra-individual variability in, and inter-individual levels of, diurnal cortisol secretion with a marker of low-grade inflammation (i.e., C-Reactive Protein; CRP). Reasoning that greater day-to-day cortisol variability could reflect a dysregulation of the HPA axis, we hypothesized that it would predict higher levels of CRP, above and beyond inter-individual differences in cortisol levels.
Methods: A 10-year longitudinal study of 130 older adults examined diurnal cortisol secretion on three different days across each of the 6 waves of data collection and levels of CRP during the last 3 waves. Indicators of mean cortisol levels, short-term cortisol variability, and long-term cortisol variability were analyzed.
Results: Hierarchical linear modeling showed significant main effects, linking baseline mean cortisol levels, *T-ratio* = 2.25, $p = 0.03$, and long-term cortisol variability, *T-ratio* = 2.63, $p = 0.01$, with higher CRP values six to ten years after study entry. In addition, a two-way interaction demonstrated that short-term variability in cortisol were associated with higher levels of CRP among individuals who secreted relatively high, *T-ratio* = 2.68, $p = 0.01$, but not low, *T-ratio* = −1.09, $p = 0.28$, baseline levels of cortisol. Finally, a three-way interaction, *T-ratio* = 2.24, $p = 0.03$, suggested that the effect of long-term cortisol variability on CRP became stronger over time among participants who secreted high average levels of cortisol, whereas it became weaker among their counterparts who secreted low average levels of cortisol.
Conclusion: Variability in cortisol secretion across days forecasts low-grade inflammation, and this association is paramount among older adults who secrete high levels of diurnal cortisol.

1. Introduction

Theory and research suggest that cortisol disturbances could link the experience of stress and disease (Cohen et al., 2007; Lupien et al., 2009; McEwen, 2007). In recent years, there has been a surge of interest in cortisol's role in modulating low-grade chronic inflammation (Miller et al., 2002; Raison and Miller, 2003), a process that is increasingly recognized as a major pathway to a number of age-related illnesses, such as coronary heart disease, diabetes, or certain cancers (Allin and Nordestgaard, 2011; Danesh et al., 2004). In fact, older adults may be at a particular risk for exhibiting patterns of cortisol and immune disturbances. For example, aging is characterized by inconsistent patterns of cortisol response to stress (Nicolson et al., 1997; Rohleder et al., 2002), greater daily cortisol levels (AUC; Nater et al., 2013; Otte et al., 2005), and greater levels of chronic inflammation and inflammatory disease (Franceschi, 2007). Thus, age-related changes in the HPA axis may influence (and be influenced by) inflammatory processes (Heffner, 2011; Straub et al., 2000) and increase vulnerability to inflammation-related diseases.

The extant research examining health-related consequences of cortisol dysregulation predominately focused on inter-individual differences in cortisol secretion, by comparing cortisol patterns between individuals obtained over the course of one day or averaged across multiple days (e.g., levels of area under the curve [AUC] or diurnal cortisol slope). This approach has revealed important insights, for example, various aspects of cortisol secretion have been shown to predict morbidity and mortality, such as high daily cortisol volume (Heim et al., 2000), both high and low serum cor-

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tisol levels (Marklund et al., 2004; Rotman-Pikielny et al., 2006), a flatter diurnal cortisol slope (Kumari et al., 2011; Sephton et al., 2013), and elevated night cortisol (Schrepf et al., 2015).

The specific links between cortisol secretion and inflammatory activity have also been considered. Synthetic preparations of cortisol have long been used in clinical settings to suppress inflammation associated with allergic, autoimmune, and other diseases. However, the doses administered in these settings are pharmacologic, and not reflective of how endogenously produced cortisol operates under physiologic conditions. In vivo, cortisol does modulate the cellular and molecular processes that underlie inflammation, but the patterns are complex (Busillo and Cidlowski, 2013). This complexity may explain why empirical studies of cortisol secretion and inflammatory processes in humans have yielded mixed findings (Chrousos, 1995; Elenkov and Chrousos, 2002; Karlović et al., 2012).

Another explanation for the mixed findings, which we address here, is that studies to date have focused on inter-individual variations in cortisol secretion, and overlooked the role of intra-individual variations. Indeed, by focusing on cortisol secretion over a single day, or aggregating scores across multiple days, potentially important differences in cortisol patterns that occur across days within different individuals are not captured (Hruschka et al., 2005). Studies that have teased apart within- and between-person differences in cortisol output over time have shown that within-person variability accounted for about 50% of the overall variation in cortisol output, indicating that there are substantial intra-individual differences in cortisol output that could be associated with health-related processes (Ross et al., 2014).

Little is known about intra-individual variability in cortisol patterns across days, or how they relate to downstream biological processes like inflammation. A degree of variability in cortisol output could mean a number of things. For example, it might reflect adaptive adjustments to changing environmental demands (e.g., as a response to a specific threat, Adam et al., 2006) and thus could be a result of co-occurring variability in stress exposure. Alternatively, unstable patterns of cortisol output could suggest an HPA axis that is responding erratically to environmental demands (Sannes et al., 2016); a possibility that would be consistent with research linking variability in successive cortisol measurements throughout the day, time-points across several days, and linear time trends with poor mental health and mood disorders (Havermans et al., 2011; Peeters et al., 2004; Sannes et al., 2016). Variability could also be part of the normative aging process, as research shows that intra-individual variability in the cortisol awakening response is greater among older as compared to younger adults (Almeida et al., 2009; Ice et al., 2004). Regardless of the cause, instability in outflow could have downstream implications for the bodily tissues that cortisol regulates, including the immunologic processes that underlie inflammation (McEwan and Stellar, 1993).

Based on the foregoing observations, the current study examined whether intra-individual cortisol variability is associated with a biomarker of low-grade inflammation, using data from a 10-year longitudinal study of community-dwelling older adults. Given the possibility that a person's typical level of cortisol might also have regulatory consequences for inflammation, these analyses simultaneously considered mean cortisol levels to account for between-person (inter-individual) differences. In addition, they explored whether mean cortisol level and intra-individual cortisol variability could interact in predicting CRP. More specifically, we predicted levels of C-reactive protein (CRP), observed 6–10 years after baseline, as an indicator of low-grade inflammation. Because intra-individual cortisol variability may increase among aging populations (Almeida et al., 2009), we compared the effects of two different indicators of cortisol variability: (1) short-term (based on three days at baseline) and (2) long-term (based on all days across waves) intra-individual cortisol variability. In addition, inter-individual differences in baseline mean levels of daily cortisol output (average AUC at T1), average mean cortisol levels across waves (average AUC across waves) and relevant covariates were included into the analyses. AUC was used as an indicator of cortisol secretion because of its previously shown associations with health-relevant outcomes (e.g., Heim et al., 2000).

2. Methods

2.1. Participants

This study is based on a sample of community-dwelling older adults who participated in the 10-year longitudinal *Montreal Aging and Health Study* (MAHS). Participants were recruited through newspaper advertisements in the Montreal area. To obtain a normative sample, the only inclusion criterion was that participants had to be older than 60 years at the time of recruitment. At baseline (T1), a total of 215 participants were assessed in their homes or in the laboratory. Participants were assessed again approximately 2 years (T2: $n = 184$), 4 years (T3: $n = 164$), 6 years (T4: $n = 136$), 8 years (T5: $n = 125$), and 10 years (T6: $n = 95$) after baseline. Study attrition was attributable to death ($n = 44$), refusal in study participation ($n = 17$), lost contact ($n = 21$), or withdrawal due to personal reasons ($n = 12$).[1]

We considered all participants for analysis who participated at T4, T5, or T6 (when CRP was assessed, $n = 143$). Thirteen participants were subsequently excluded because they did not provide useable data for either baseline cortisol ($n = 4$) or for CRP at T4, T5, or T6 ($n = 9$). The analytic sample thus included 130 participants. Excluded participants were significantly older at baseline ($M = 73.94$, $SD = 6.91$) than those who remained in the study ($M = 71.42$, $SD = 4.93$; $t[139.10] = -2.92$, $p < 0.01$). Excluded participants did not significantly differ from other participants on any of the other baseline measures used in this study ($|ts| < 1.09$, $ps > 0.05$).

2.2. Materials

2.2.1. C-Reactive protein (CRP)

C-reactive protein (CRP) was assessed as a measure of low-grade inflammation at T4–T6 by collecting dried blood spots. Single-use lancets were used to deliver a uniform puncture to the finger and up to three drops of blood were collected on a filter paper (McDade et al., 2004). The filter paper was allowed to dry and stored in a freezer at −20 °C degrees. After completion of each study wave, the samples were analyzed in the Laboratory for Human Biology Research at Northwestern University, using a high-sensitivity enzyme immunoassay (Williams and McDade, 2009). Validation studies measuring CRP from finger-prick dried blood spots have shown high correlations (e.g., $r > 0.85$) with matched CRP samples derived from venous blood, as well as good sensitivity and reliability (McDade et al., 2004). The averaged inter-assay coefficient of variation across waves was less than 8.7%. Three single CRP scores were excluded from the analysis because they were higher than 10 mg/L, which is likely to indicate acute infections (Pearson et al., 2003). Of the included participants, 120 participants at T4 reported valid CRP scores, 102 participants at T5, and 81 participants at T6.

[1] Associations with CRP have been reported in a previous manuscript from the MAHS (Rueggeberg et al., 2012). However, the previous study only included CRP values from wave 4, and did not examine cortisol variability as a main predictor variable.