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Chronic stress, hair cortisol and depression: A prospective and longitudinal study of medical internship

Stefanie E. Mayer[a,b,*], Nestor L. Lopez-Duran[a], Srijan Sen[b], James L. Abelson[b]

[a] Department of Psychology, University of Michigan, 530 Church Street, Arbor, MI, 48109, USA
[b] Department of Psychiatry, University of Michigan, 4250 Plymouth Rd, Ann Arbor, MI, 48109, USA

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ABSTRACT

Background: Stress plays a causal role in depression onset, perhaps via alteration of hypothalamic-pituitary-adrenal (HPA) axis functioning. HPA axis hyperactivity has been reported in depression, though inconsistently, and the nature of this relationship remains unclear, partly because cortisol measurement over time has been challenging. Development of hair cortisol assessment, a method that captures cortisol over prolonged periods of time, creates new possibilities. In this study, hair cortisol was incorporated into a prospective and longitudinal study of medical internship, stress and symptoms of depression. This provided a rare opportunity to 1) prospectively assess hair cortisol responses to stress, and 2) examine whether stress-induced changes in hair cortisol predict depressive symptom development.

Methods: Hair cortisol, depressive symptoms, and stress-relevant variables (work hours, sleep, perceived stress, mastery/control) were assessed in interns (n = 74; age 25–33) before and repeatedly throughout medical internship.

Results: Hair cortisol sharply increased with stressor onset, decreased as internship continued, and rose again at year's end. Depressive symptoms rose significantly during internship, but were not predicted by cortisol levels. Hair cortisol also did not correlate with increased stressor demands (work hours, sleep) or stress perceptions (perceived stress, mastery/control); but these variables did predict depressive symptoms.

Discussion: Hair cortisol and depressive responses increased with stress, but they were decoupled, following distinct trajectories that likely reflected different aspects of stress reactivity. While depressive symptoms correlated with stressor demands and stress perceptions, the longitudinal pattern of hair cortisol suggested that it responded to contextual features related to anticipation, novelty/familiarity, and social evaluative threat.

1. Introduction

Depression affects 16% of Americans at some point during their lives (Kessler et al., 2005) and represents the single largest contributor to global disability according to the World Health Organization (WHO, 2017). Life stress is the most common causal trigger of depression onset (Kendler et al., 1999). Understanding how life stress leads to depression can further our understanding of the disorder and inform prevention strategies. One potential pathway involves the hypothalamic-pituitary-adrenal (HPA) axis and its end product cortisol (Taylor et al., 1997). HPA axis hyperactivity has been linked with depression (reviewed in Nemeroff and Vale, 2005), but variations exist (e.g., depending on patient and clinical factors; Lamers et al., 2013; Stetler and Miller, 2011) and the temporal nature of this relationship is still unclear. There is some evidence that HPA axis dysregulation may precede depression (Adam et al., 2010; Harris et al., 2000), but interactions with chronic stress exposure are rarely examined.

The HPA axis is a complex system that is shaped by and interacts with psychosocial (Levine, 2000), contextual (Gunnar et al., 2009), genetic (Gotlib et al., 2008), and developmental factors (Tyrka et al., 2008). This system helps us respond to acute stress, but it also undergoes long-term changes in response to repeated stress experiences. These longer-term alterations may be particularly relevant in the etiology of depression (Ehlert et al., 2001). Tracking HPA activity over time holds the potential to illuminate its role in depression. However, quantification of longer-term HPA axis activity has been notoriously difficult as traditional cortisol measures in blood, saliva, or urine only capture activity over a period of minutes to hours and are sensitive to numerous confounding variables (reviewed in Russell et al., 2012). These methodological challenges have hampered efforts to understand the links between stress exposure, longer-term HPA activity, and depression onset.

* Corresponding author: Department of Psychiatry, University of California San Francisco, 3333 California St, Suite 465, San Francisco, CA, 94118, USA.
E-mail addresses: Stefanie.Mayer@ucsf.edu (S.E. Mayer), nestorl@umich.edu (N.L. Lopez-Duran), srijan@med.umich.edu (S. Sen), jabelson@med.umich.edu (J.L. Abelson).

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Development of hair cortisol assessment, a method that quantifies cumulative cortisol production over prolonged periods of time, creates new research possibilities. It has been validated in clinical and non-clinical contexts to reflect systemic long-term cortisol exposure (retrospectively, up to 6 months; Gow et al., 2010). It also may allow us to assess stress-induced changes in cortisol exposure longitudinally, over months to years, which could provide insights into the role of HPA axis functioning in depression. Cross-sectional studies have shown elevated hair cortisol in stressed populations (Stalder et al., 2017; Staufenbiel et al., 2013), but prospective studies that assess within-person *changes* in hair cortisol accumulation in the context of long-term stress exposure are lacking. Some cross-sectional studies have also shown positive associations between hair cortisol and clinically diagnosed depressed patients (mostly inpatients; Dettenborn et al., 2012) as well as between hair cortisol and self-reported depressive symptoms in non-clinical community samples (Abell et al., 2016; Faresjo et al., 2013; Stalder et al., 2014; Wikenius et al., 2016). However, the first meta-analytic review, which included primarily cross-sectional studies, did not show consistent links with self-reported depressiveness (Stalder et al., 2017). Prospective stress designs are needed to determine the temporal relationships between chronic stress, long-term HPA axis activity, and depressive symptoms. Because stress, by its nature, is unpredictable and heterogeneous, such studies have been difficult.

Medical internship—the first year of professional clinical training for physicians following medical school graduation—provides a naturalistic chronic stress paradigm. It is a time of high stress (Butterfield, 1988) and meta-analytic evidence (54 studies; n = 17 560 resident physicians) estimates an overall prevalence of depression during residency of 28.8%, ranging from 20.9% to 43.2% (Mata et al., 2015). Medical internship allows for prospective tracking of perceived and experienced stress and the development of depression, starting before stressor onset, and with longitudinal follow-up throughout the 12 months of internship exposure. The somewhat homogenous sample facing a relatively "standardized" stressor may provide a paradigm with reduced "noise" that might otherwise obscure linkages.

The combination of hair cortisol technology and the internship model allows us, for the first time, to prospectively assess how chronic stress exposure affects HPA axis functioning and determine whether stress-induced changes in HPA axis functioning are linked to depressive symptom development. Based on previous cross-sectional studies, we hypothesized that 1) hair cortisol levels will significantly increase with internship stress and 2) the increase in cortisol levels will associate with an increase in depressive symptoms.

2. Material and methods

2.1. Participants

The study was part of an ongoing longitudinal study of depression during medical internship (Sen et al., 2010). Participants were recruited from graduating University of Michigan Medical School students who matched to attend internship within 50 miles of Ann Arbor to allow in-person collection of hair samples and to control for other pre-internship stressors (e.g., moving). Participants were required to have a minimum hair length of 1 cm. They signed written consent and were paid $350 for study participation. We collected data from residency cohorts over a 4-year period from 2012 to 2015 (2012: n = 18, 2013: n = 23, 2014: n = 14, 2015: n = 19), yielding a final sample of 74 participants. The study was approved by our local Institutional Review Board (IRB).

2.2. Procedures and measures

2.2.1. Hair assessment

Hair samples were collected 1–2 months prior to internship start (pre-internship) and at the four-, eight- and twelve-month time points during internship year, following guidelines from the Society of Hair Testing (Cooper et al., 2012). At each hair collection time point, 2–3 hair samples were cut with scissors from the posterior vertex region of the head (cut close to the scalp without pulling hair; all collected hair samples were analyzed). After hair collection, samples were wrapped in aluminum foil and stored at room temperature (Gow et al., 2010). Annual collections were analyzed in batches, such that when the last hair sample was obtained at the end of a given internship year (cohort), all samples of that year were sent to Dr. Kirschbaum's laboratory at the Dresden University.

Starting at the scalp-near end, samples were cut into two 2–cm segments for analysis (where length permitted; mean segment weight was 5.5 mg ± 0.5 mg). Hair growth rates vary between individuals (Schütz et al., 1993), but a rate of 1 cm/month has been generally accepted in the literature for a 1–cm hair segment (Schütz et al., 1993; Wennig, 2000). The first 2–cm segment (Segment 1) thus reflects total cortisol production over the 2 months prior to the collection time point; the next 2–cm segment (Segment 2) reflects secretion during months 2–4 before the collection time point. When we subsequently refer to hair cortisol levels at a specific time point, these actually reflect cortisol secretion over the prior months as described above. Hair samples were assayed for cortisol using a validated, commercially available immunoassay with chemiluminescent detection (procedures are described in more detail in Stalder et al., 2012).

2.2.2. Self-report measures

Participants provided *socio-demographic* (sex, age, ethnicity, marital status, having a child, medical specialty), *health-related* (Body Mass Index—BMI, smoking, antidepressant use, oral contraceptive use, personal history of depression, family history of depression, stressful life events in the past 3 months), and *hair-related information* (hair color, use of hair products, hair coloring/dying/bleaching/perm, weekly hair washing frequency).

Self-reported *depressive symptoms* in the past 2 weeks were assessed prior to internship start and at three-month intervals during internship using the 9-item Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001). *Perceived stress* and *sense of mastery/control* were measured prior to internship start and at four-month intervals during internship using the 10-item Perceived Stress Scale (PSS; Roberti et al., 2006) and Pearlin's 7-item Mastery Scale (Pearlin and Schooler, 1978), respectively (only available for cohorts 2013–2015). Other *internship information* (e.g., sleep hours/night in the past week, weekly work hours, days off in the past month) was also collected at pre-internship and during quarterly assessments.

2.3. Statistical analyses

2.3.1. Data preparations

No outliers were excluded from analyses to avoid data loss, but extreme hair cortisol values at the upper 5% of the distribution were winsorized (set at the 95 percentile value) to reduce their impact on data analyses (Adam and Kumari, 2009; Wilcox, 1998). The winsorized hair cortisol raw data is presented in Fig. 1. Hair cortisol values and depressive symptoms (PHQ-9 scores) were log transformed to improve skewness and kurtosis. Hair cortisol concentrations between the first and the second 2-cm segments were highly correlated, but not identical (BL: $r = 0.875$, 4-months: $r = 0.912$; 8-months: $r = 0.819$; 12-months: $r = 0.715$). We analyzed both segments to examine hair cortisol concentrations throughout the entire internship year, testing links with stress exposure, psychosocial stress, and depressive symptoms. Generally, correlations of hair cortisol values between time points ranged from $r = 0.4$ to $r = 0.9$, suggesting both intra-individual stability, but also individual variability over time.

There is some loss of cortisol signal over time (reflected in declining concentrations farther from the scalp), possibly due to wash-out effects (Kirschbaum et al., 2009). Three independent, published samples report cortisol decline rates per 1-cm hair segment of 2.5 pg/mg (Kirschbaum