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Individual differences in the diurnal cycle of salivary free cortisol: a replication of flattened cycles for some individuals

Arthur A. Stone [a,*], Joseph E. Schwartz [a], Joshua Smyth [b], Clemens Kirschbaum [c], Sheldon Cohen [d], Dirk Hellhammer [c], Steven Grossman [a]

[a] *Department of Psychiatry and Behavioral Science, State University of New York at Stony Brook, Putnam Hall, Stony Brook, NY 11794-8790, USA*

[b] *Department of Psychology, North Dakota State University, Fargo, ND 58105, USA*

[c] *Center for Psychobiological and Psychosomatic Research, University of Trier, Building D, D-54286 Trier, Germany*

[d] *Department of Psychology, Carnegie-Mellon University, Pittsburgh, PA 15213, USA*

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Abstract

Free cortisol measured in saliva has been shown to have the same diurnal rhythm as serum cortisol, one that typically declines rapidly throughout the waking day. A recent study showed that over 15% of a sample of community individuals who were monitored over two days did not show the typical diurnal rhythm. The present study specifically tested the hypothesis that there is significant between-subject variation (individual differences) in diurnal rhythms using multi-level, random regression models. Analyses of participants from four studies were conducted; studies varied in terms of the number of saliva samples taken per day, the number of days studied, and participants' demographic and health status. Significant individual differences of diurnal cycle in each of the four samples were found. In at least 10% of each sample no significant diurnal cycles was detected; however, the overall mean level of cortisol of those with flat cycles differed among the samples. These results suggest that some people do not have the expected diurnal rhythm of cortisol secretion. It is not clear what the determinants of this finding are or if there are any health consequences of having a flat cycle.

Keywords: Cortisol; Diurnal cycle; Individual differences

* Corresponding author. Tel.: +1-631-632-8833; fax: +1-631-632-3165.
E-mail address: arthur.stone@sunysb.edu (A.A. Stone).

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Cortisol is a hormone secreted by the hypothalamic–pituitary–adrenal (HPA) axis that plays a number of important functions in humans. It affects glucose production, fat metabolism, inflammatory responses, vascular responsiveness, and central nervous system and immune functioning. As such, the HPA axis and cortisol levels have been implicated in both psychiatric and somatic illness, including depression, post-traumatic stress disorder, eating disorders, hypertension, hyperlipidemia, hypercholesterolemia, sexual dysfunction, immunosuppression, and many others (Chrousos and Gold, 1998; Heim et al., 2000; McEwen, 1998; Yehuda, 1997).

Regulatory mechanisms of the HPA axis are of considerable concern because they may be related to HPA axis dysfunction. One of the strongest regulators of many hormones, including cortisol, is the circadian timing system (Czeisler and Klerman, 1999). Examination of the diurnal cycle and deviations from the cycle may provide clues as to the physiological (e.g., females have a less pronounced cortisol response; Kirschbaum et al., 1992, 1999) and environmental influences (e.g., protein-rich meals increase cortisol production; Follenius et al., 1982) on the HPA axis. Symptoms of at least some chronic diseases — asthma and rheumatoid arthritis — have been shown to be linked to hormonal rhythms, and other research has shown altered cycles in some patient groups (rheumatoid arthritis and fibromyalgia; McCain and Tilbe, 1989).

HPA axis hormones show a well-documented circadian rhythm resulting from stimulation of paraventricular neurons by pacemaker cells located in the suprachiasmatic nucleus. CRH, ACTH and cortisol are secreted in pulsatile fashion with a clear-cut on–off pattern. For the end-point of the HPA axis, cortisol, 10–15 secretory episodes occur over 24 h with the strongest secretory activity of the adrenal cortex during the early morning hours in day-active individuals. Peak cortisol levels are observed shortly after awakening with steadily decreasing values thereafter in the absence of significant external stimulation. The trough of cortisol secretion is reached around midnight with only minimal levels of this steroid detectable (Anders, 1982; Desir et al., 1980; Weitzman et al., 1971). This is a particularly robust diurnal pattern, one that we expect should be displayed by most non-ill individuals experiencing typical daily life (alterations are expected in those individuals subjected to environmental extremes; e.g., torture, extreme psychological distress, major alterations in diet, nightshift workers etc.; e.g., Deinzer et al., 1997; Opstad, 1992; Rahe et al., 1990).

A previous study conducted by our group (Smyth et al., 1997) examined a group of community-dwelling individuals. Selected to test the effects of chronic unemployment on cortisol levels, 109 adults gave six saliva samples at random points throughout the day for two consecutive days. Patterns of diurnal cycles were estimated for each of the two days and participants were classified according to these patterns. Fifty-one percent of the sample showed strong, decreasing patterns of cortisol on both days, 31% showed inconsistent cycles where one day was typical and the other flattened, and 17% showed flattened cycles on both days. The flattened cycles had, in absolute terms, slopes that approached zero. This was a surprising observation considering it suggests variability in a process that is believed to be relatively homogeneous, with the exception of certain medically or psychiatrically ill individuals.

Absence of a diurnal cycle could possibly be indicative of a dysregulation of the HPA axis due either to associated physiological phenomena or to altered environmental circumstances.

The Smyth et al. (1997) result is potentially important and additional studies are needed to confirm and extend it. First, as with all new findings, this result requires replication to ensure that it is not simply a spurious observation. Second, although six samples of cortisol per day may appear adequate for the task of defining cycles, characterization of a cycle can be unduly altered by one or two measurements that deviate from the overall diurnal slope. As mentioned above, this can happen for a number of reasons, including meals, exercise, emotional upset, or to simple chance factors, although such factors were not found in the Smyth et al. (1997) study. The fewer the number of samples analyzed per day, the greater the potential impact of this effect. Third, we originally studied only two days and, although we were encouraged by the consistency over the two days, we would like to know if flattened cycles would emerge over a longer period of time. Once again, it is possible that for some individuals an unusual event spanning two days was responsible for the results previously reported.

In this report we conduct secondary data analyses of four studies that enable us to address the issues raised above. The first study was conducted by Kirschbaum and colleagues (Kirschbaum et al., 1999) in which college student participants collected saliva every 30 min over the course of 12 waking hours for a single day. Concern about a small number of unreliable points biasing the diurnal slope is not a concern in this study given the extremely high cortisol sampling density. The study design does not, however, address concerns about daily variation of cycles. The second study was also conducted by Kirschbaum and colleagues (Kirschbaum et al., 1994). It was more comprehensive in that 49 saliva samples were collected on each of two days, but from only 20 individuals. A third study by Cohen and colleagues examined cortisol secretion on non-consecutive days with nine saliva collections per day. There was an interval of seven days between the first and second sampling day. The fourth sample was obtained in the context of a randomized controlled trial of a writing treatment for rheumatoid arthritis patients (Smyth et al., 1999). Patients in this study were examined seven days prior to the treatment, during the three days of treatment, and 14 days subsequent to treatment. One-third of the patients were assigned to a control condition and the remainder to the experimental condition. On each of 24 days, saliva samples were collected once in morning, afternoon, and evening. This sample has the strength of enabling examination of cyclicity over many days, yet has the weaknesses of only three saliva samples per day and the potential confound of the disease process and medications on cortisol levels.

A positive feature of this paper is the way that diurnal cycles were analyzed. Our previous methods made use of ordinary least square (OLS) regressions computed on each subject and on each day. Slope estimates were then examined and classified by the authors using loosely defined criteria. More appropriate methods of analyzing these data are available that explicitly account for the multiple levels of the design (momentary saliva samples nested within days which are nested within subjects) and autocorrelation of residuals. Recently, Schwartz and Stone (1998) have discussed

the use of multi-level or random regression models for analyzing these sorts of data. This approach has the advantage of eliminating the need for arbitrary investigator decisions as it explicitly estimates and tests the between-person variation in diurnal cycle.

Our first hypothesis is that strong diurnal cortisol cycles will be detected in each of the four samples, replicating previous work. The second hypothesis is that random regression models of individual diurnal cycles will yield significant variation among persons (individual differences). Testing this hypothesis is critical, because there will always be random variation of cycles in samples, but not necessarily statistically significant variation. Only if cycle variation is significant will we be justified in testing the final hypothesis. Our third hypothesis is that if significant variation is detected, we will uncover a subset of individuals in each sample that has a flat diurnal cycle.

1. Methods

1.1. Description of samples and data collection methods

1.1.1. Kirschbaum study 1: 66 participants, 25 saliva samples per day, 1 day

Eighty-one healthy male and female volunteers between 18 and 32 years of age were recruited for a study on the impact of gender, oral contraceptives, and menstrual cycle phase on the reactivity of the HPA axis. A total of 66 subjects completed collection of circadian salivary cortisol profiles and returned the saliva samples to the laboratory. This study sample was composed of 14 men (48%), 15 women in the follicular phase (days 4–7) of the menstrual cycle, 17 women in the luteal phase (days 21–25) and 20 women who had used oral contraceptives (OC; monophasic formulas, ethinyl estradiol content: <50 μg) for at least six months. Menstrual cycle phase was validated post hoc endocrinologically by measurement of estradiol and progesterone levels. A total of 25 saliva samples were taken by each participant at 30 min intervals between 9 am and 9 pm. Before entering the study all subjects had to provide written consent and underwent a comprehensive medical examination for past and current health problems. Smokers, subjects suffering from allergies and women with irregular menstrual cycles or using multi-phasic oral contraceptives were excluded.

Saliva samples were collected using a special device (“Salivette”, Sarstedt, Rommelsdorf, Germany). Briefly before assaying, saliva samples were thawed and spun at 3000 rpm for 5 min to obtain saliva samples with low viscosity. One hundred microliters of clear saliva was removed for duplicate analysis of cortisol levels using a time-resolved immunoassay with fluorescence detection (Dressendörfer et al., 1992). The lower detection limit of this assay is 0.43 nmol/l with inter- and intraassay coefficients of variance of less than 10% across the expected range of cortisol levels (3–25 nmol/l). These saliva collection methods and assays were the same for all four studies.

1.1.2. Kirschbaum study 2: 20 participants, 49 saliva samples per day, 2 days

Ten healthy male smokers (>15 cigarettes per day) and 10 healthy male non-smokers participated in this study (average age: 25 years). They were recruited for an investigation of the effect of smoking on the reactivity of the HPA axis. On two consecutive days, participants collected saliva samples at 15-min intervals between 9 am and 9 pm. Before entering the study all subjects had to provide written consent and underwent a comprehensive medical examination for past and current health problems. Volunteers suffering from any chronic disease were excluded from participation.

1.1.3. Cohen study: 176 participants, nine saliva samples per day, 2 days

Healthy 18–55-year-old subjects were recruited through advertisements in local newspapers to participate in a study on determinants of susceptibility to upper respiratory infections. All underwent thorough physical exams with extensive laboratory tests to guarantee they were in excellent health. All were instructed on techniques for collecting saliva and samples were collected in subjects' natural settings on two weekdays prior to being challenged with a virus. Saliva samples were collected at wake-up and at other predetermined lags relative to wake-up: plus 1, 2, 4, 6, 8, 10, 12, 14, and 16 h after wake-up. The wake-up saliva sample was excluded from analysis in order that our estimate of the decline in cortisol during the awake period would not be attenuated by the fact that cortisol rises steeply during the first 30–60 min after awakening. A preprogrammed wrist watch (programmed on the basis of their usual waking time) signaled the subject when to provide saliva samples. Each signal was accompanied by a numeric code that the subject wrote on the collection tube. Data were collected from 272 subjects. However, the analyses are restricted to 176 who completed 90% or more appropriately coded saliva samples during collections. There were no differences between the original sample and the group meeting collection criteria on age, gender, race, education, or body mass. Fifty-three percent were male, the average age was 29.6 (SD=10.7), 65% were white, and 56% completed at least some college.

1.1.4. Smyth study: 47 participants, three saliva samples per day, 24 days

Rheumatoid arthritis patients were recruited from a local rheumatology practice and participated in a study comparing structured writing about stressful events with a time management control condition. A total of 243 patients were screened and 49 were eventually enrolled in the study (see Smyth et al., 1999, for details). Average age of the sample was 51 years, 71% were female, 96% were white, and the average number of years of education was 14.1. Patients taking significant doses of corticosteroid medications were excluded. Saliva samples were collected seven days prior to the interventions, during the three days of intervention, and for 14 days following the intervention. Those saliva samples collected during the three days of the intervention were excluded from analyses. At randomly selected times in the morning, afternoon, and evening patients were signaled via a preprogrammed wrist watch to take a saliva sample, yielding a maximum of three saliva samples per day.

2. Results

Random coefficient regressions were used to model the diurnal cycle of cortisol in our samples (Schwartz and Stone, 1998). Conceptually, each person's cortisol data were regressed against time-of-day. When multiple days of assessment were available in a study (i.e., not for Kirschbaum study 1 with only one day), a pooled estimate of the average slope, allowing for random day-to-day variability, was estimated. Two versions of each model were computed for each study. In the first, participants were treated as a random factor and estimates of the inter-subject variability of intercepts and slopes were obtained. If estimates for slope variability were significant, indicating the existence of variation of slopes in the general population, we then estimated a second model. In this model, participants were treated as a fixed factor in order to obtain maximum likelihood estimates of each individual's intercept and slope. These estimates were used to examine the distribution of intercepts and slopes and to determine whether a subset of individuals had flat or nearly flat diurnal patterns. As has been the procedure in prior studies, all analyses were computed on log-transformed cortisol values.

Table 1 presents a summary of both the random effect modeling and the fixed effect modeling for all four studies. The average intercepts and slopes are almost identical in the fixed and random models. These statistics define the overall diurnal cycle of cortisol in the groups, which are shown graphically in Fig. 1. Observed cycles are surprisingly similar given the variability among samples and methodologies employed among the four study designs. Their overall shape is typical of patterns previously shown in the literature and confirm our first hypothesis.

Our second hypothesis was that significant variability among slopes would be observed in each study. Variability estimates and significance testing are shown on the third line in the random effects section of Table 1. Standard deviations for the slope in each of the four studies were significantly greater than zero, indicating systematic variation of the slopes. Confirmation of the second hypothesis allowed us to explore the magnitude of slopes at the extremes of the distribution.

The third hypothesis was that a subgroup of individuals in each study would exhibit flat diurnal cycles of cortisol. To test this hypothesis, we examined subgroups of individuals at the lower and upper ends of the slope distribution. Average slopes for the lowest 10% of each sample and for the highest 10% of the sample are shown toward the bottom of Table 1 and are presented graphically in Fig. 2. Analyses of the remaining participants, those not in either the upper or lower decile, are shown in Fig. 2 and are labeled as the middle eight deciles. The slopes of the diurnal cycle for the 10% with the least steep slopes are essentially flat in two of the samples, and almost flat in the other two samples. A weakness of this analysis is the small number of individuals comprising the extreme groups. We therefore created another set of groups with the smallest slopes, but expanded the criteria to include the lowest 20% of each distribution. These data are presented in the last three lines of Table 1.

Table 1
Random coefficient regression results

	Study			
	Kirschbaum 1	Kirschbaum 2	Cohen	Smyth
$N_{persons}$	66	20	176	39
Assessments per day	25	49	9	3
Observed assessments per day	24.9	48.9	8.9	2.5
Random model				
Avg slope	−0.11	−0.11	−0.10	−0.09
95% conf. int.	−0.12, −0.10	−0.13, −0.09	−0.11, −0.09,	−0.11, −0.07
Standard deviation of slopes[a]	0.04	0.04	0.04	0.06
Fixed model				
Avg slope	−0.11	−0.11	−0.10	−0.09
95% conf. int.	−0.12, −0.10	−0.13, −0.09	−0.11, −0.09	−0.11, −0.07
Avg slope of bottom decile (*n*)	−0.04 (7)	−0.05 (2)	0.01 (18)	0.00 (4)
Avg slope of top decile (*n*)	−0.19 (7)	−0.20 (2)	−0.19 (18)	−0.23 (4)
Avg slope of bottom quintile (*n*)	−0.05 (13)	−0.05 (4)	−0.01 (35)	−0.01 (8)
Avg slope of top quintile (*n*)	−0.17 (13)	−0.17 (4)	−0.17 (36)	−0.19 (8)

[a] All slope variability estimates are significant at $p<0.0001$, except for the Kischbaum study 2 where $p<0.04$.

3. Discussion

Our goal was to replicate our previous result that a substantial number of individuals, who were not selected for any explicit disturbance of the endocrine system, had flat diurnal patterns of salivary cortisol. To maximize the generalizability of the results, data from four studies of salivary cortisol were re-analyzed using random regression modeling techniques. The studies varied in terms of the number of saliva samples taken each day (3–49), the number of days participants were studied (1–24), their average ages (25–51), and their health status (healthy or having a chronic illness).

In spite of the heterogeneity among the sample characteristics, a remarkable consistency of results was observed. Analyses clearly confirmed our three hypotheses. We first replicated previous findings of a strong diurnal cycle of cortisol in the natural environment. Second, we detected significant individual variation in diurnal cortisol slopes for each of the studies and the standard deviations of slopes were substantial. This means that it is not reasonable to expect that the average diurnal rhythm for a sample adequately represents the rhythm of each individual in the sample. When we

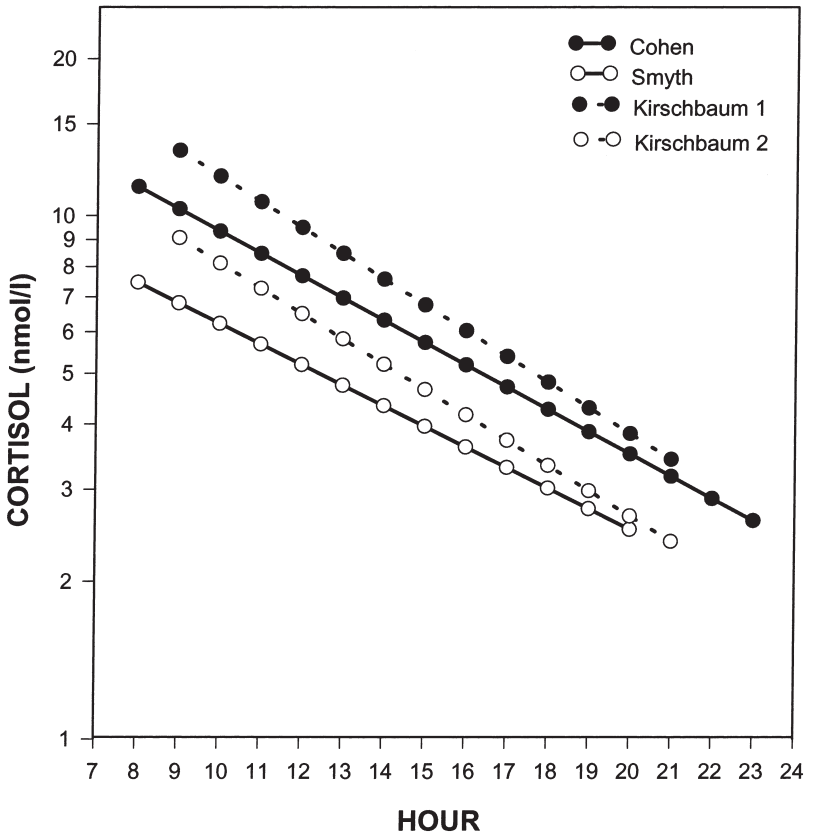

Fig. 1. Diurnal cycle for the four studies derived from regression analyses. Cortisol (*y*-axis) is plotted on a logarithmic scale.

examined the lower (flatter) 10 and 20% of the rhythm distribution, we found that these subgroups of individuals had almost no linear component to their cycles. However, there was some variation in these slopes among the four samples. In both of the Kirschbaum samples, who were college students intensively studied for 1 or 2 days, the 10th percentile group had an average diurnal slope that was slightly negative, whereas the slopes of the remaining two samples showed absolutely no evidence of a negative slope. A similar pattern of results emerged when the lower 20% of the rhythm distribution was examined.

Another aspect of the observed rhythms is of interest, although it is something that we did not consider a priori. Although all four samples showed evidence of a flattened diurnal rhythm, the morning levels among the sub-samples varied considerably. In both Kirschbaum samples, the flattened groups exhibited the typical elevation of morning cortisol levels, whereas the flattened groups in the other two studies had much lower morning levels (see Fig. 2). The differences in these patterns may suggest avenues for approaching the etiology and mechanisms causing the flattening.

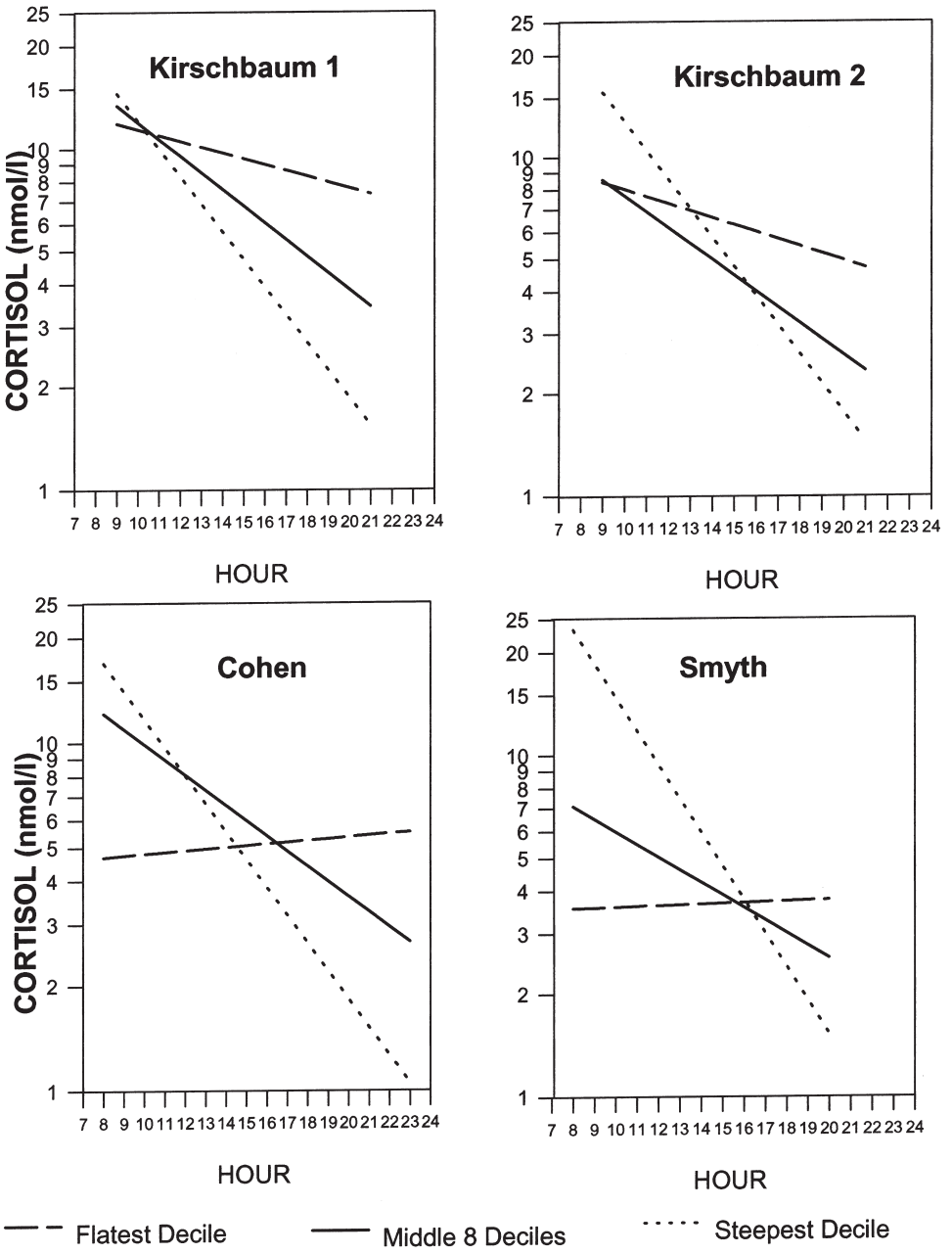

Fig. 2. Diurnal cycles for upper and lower 10th deciles and middle eight deciles for four studies. Cortisol (*y*-axis) is plotted on a logarithmic scale.

For example, we know that certain physical and social stressors significantly elevate cortisol levels in the laboratory (e.g., public speaking, Bassett et al., 1987; Kirschbaum et al., 1993a; and exercise, Mason et al., 1973; Kirschbaum et al., 1993b). It is plausible that these activities are associated with the diurnal cycle in such a way that they could alter cortisol rhythm. For example, the Kirschbaum samples were of young adults (students) whereas the Cohen and Smyth samples were of middle-aged adults. There could also be physiological alterations of the HPA regulatory systems in these individuals that might be explored with HPA axis challenge tests.

Despite the consistency of the findings across the four samples, we must also take into consideration the fact that little is known about the reproducibility of diurnal rhythms over longer periods of time, namely, months or years. It is clearly premature to conclude that those individuals with flat cycles in these analyses will consistently maintain those flat cycles (notably, this information is also not available for daily level of cortisol secretion as well). The degree of temporal stability is of considerable conceptual importance for interpreting any health consequences of the altered cycle: transient flattened cycles that revert to typical cycles are less likely to be of importance than very stable flattened cycles.

Although we have only alluded to the possible health implications of the flattened diurnal cycles in the introductory materials, Spiegel and colleagues (Sephton et al., 2000) have recently published the results of a breast cancer clinical trial where cortisol rhythms were examined. Women who had relatively flat diurnal cycles died significantly earlier than women with more typical cycles, even after standard risk factors were statistically controlled. Given the nature of the sample and altered physiology that such patients may have, we view these results cautiously. Nonetheless, they do provide an indication that cortisol cyclicity may be a variable worthy of further study.

Overall, we interpret these findings as supportive of the hypothesis that there are some individuals who, at least in the short-term, have flat diurnal cycles of cortisol. As stated above, several factors suggest caution in interpreting the results, including our lack of knowledge about the stability of the results and of the mechanism responsible for them. Future research should examine the correlates of individual differences in cortisol rhythms, including social, psychological, genetic, and biological factors.

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