Diurnal Cortisol Rhythms: Social Determinants and Role as a Risk, State or Scar Marker for Major Depressive Disorder in Youth

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General Research Question

How everyday social and emotional experiences “get under the skin” to influence biology, health and developmental outcomes?
Chronic Social and Emotional Stress:
Social Isolation, Interpersonal Conflict, Loss, Violence Exposure, Discrimination

Socioeconomic and Policy Environment

Ongoing Supports/Buffers:
Community and Family Supports
Individual Coping Resources

Daily Social and Emotional Experiences, Daily Activities

Physiological Stress System Activity (HPA axis)

Sleep Processes

Disparities in:
Emotional Health
Physical Health
Academic Outcomes
Cortisol Diurnal Rhythm and its “Markers”

**CAR** = wakeup + 40 min minus wakeup cortisol

**AUC** = area under curve across waking day

**Slope** = average rate of decline from wakeup to bedtime (w/o CAR)

**CAR** = wakeup + 40 min minus wakeup cortisol

**AUC** = area under curve across waking day

**Reactivity** = cortisol higher than expected for that time of day for that person
Different Cortisol Parameters:

- Measure distinct aspect of cortisol activity
- Are differentially influenced by psychosocial events
- Are differentially related to developmental and health outcomes
- Are potentially regulated by different neurobiological pathways and have different neurobiological impacts
- May change over differing time scales
- Will illustrate with examples from my study of the development of major depressive disorder in youth
Youth Emotion Project

- Longitudinal study of factors contributing to the emergence of emotional disorders over the transition to adulthood
- Youth oversampled for risk for emotional disorder based on high levels of neuroticism
- Diverse sample recruited age 17, followed for 4 + years

- Full study: N=627
- Cortisol study: N=300
Measures (repeated yearly)

- **HPA axis activity / cortisol**
  - Salivary cortisol, 6x per day for 3 days

- **Momentary and daily stress**
  - ESM diary method, 6x per day for 3 days

- **Chronic and Episodic Life Stress**
  - Hammen’s Life Stress Interview

- **Psychopathology**
  - SCID diagnostic interview
  - DSM IV diagnoses of Mood and Anxiety Disorders and Comorbid Mood and Anxiety

- **Sleep Timing and Quality via Actigraphy**
## Data Overview (Cross-sectional Models)

<table>
<thead>
<tr>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life stress</td>
<td>Life stress</td>
<td>Life stress</td>
<td>Life stress</td>
</tr>
<tr>
<td>Sleep</td>
<td>Sleep</td>
<td>Sleep</td>
<td>Sleep</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Cortisol</td>
<td>Cortisol</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Emotional Disorder</td>
<td>Emotional Disorder</td>
<td>Emotional Disorder</td>
<td>Emotional Disorder</td>
</tr>
</tbody>
</table>
Loneliness and Cortisol
(Doane & Adam, 2010, PNEC, 35, 430-441)

- To what degree are state (momentary and daily) and trait (typical) experiences of loneliness related to cortisol levels?

- Three Level Hierarchical Linear Growth Models
  - Level 1: Momentary Cortisol and Emotions
  - Level 2: Day Level Predictors
  - Level 3: Person Level Predictors and Covariates
Dependent variable: momentary cortisol

Youth with high levels of chronic interpersonal life stress → Higher level of momentary cortisol when higher momentary loneliness
Higher Levels of loneliness the day before...

Youth with increased levels of loneliness the day before have 26% greater CAR the next morning.

Doane, Adam et al., 2010, PNEC
(replicates Adam et al., 2007, PNAS)
Flatter diurnal rhythm for youth with high levels of trait loneliness

Youth with avg. levels of Trait Loneliness

Youth with 1SD higher levels of Trait Loneliness

Cortisol (μg/dl)

Time of Day
Diurnal Rhythm by Psychopathology

Cortisol (μg/dl) vs Time of Day

- No Psychopathology
- C. CoMorbid

* Significant difference
Psychopathology and Affective Experiences

*Flatter slope = state marker?*

Differences in affect and stress mediate associations between current MDD and cortisol slopes

Doane, Adam, et al., Submitted
Diurnal Rhythm by Past MDD

Youth without MDD

Youth with MDD

Cortisol (μg/dl)

Time of Day

Wake Up
Wake Up+30
Beep 1
Beep 2
Beep 3
Bedtime

-Not explained by current affective experience
=SCAR MARKER?
Data Overview (Longitudinal Models)

Wave 1
- Life stress
- Sleep
- Cortisol
- Emotional Disorder

Wave 2
- Life stress
- Sleep
- Cortisol
- Emotional Disorder

Wave 3
- Life stress
- Sleep
- Cortisol
- Emotional Disorder

Wave 4
- Life stress
- Sleep
- Cortisol
- Emotional Disorder
### Longitudinal Prediction of New Cases of Mood Disorders

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$\beta$</th>
<th>$p$-value</th>
<th>Exp($\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Emotion on Days of Cortisol Testing</td>
<td>.675</td>
<td>.053</td>
<td>1.965</td>
</tr>
<tr>
<td>Chronic Relationship Stress</td>
<td>.198</td>
<td>n.s.</td>
<td>1.219</td>
</tr>
<tr>
<td>Episodic Stress</td>
<td>.910</td>
<td>.011</td>
<td>2.485</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>.740</td>
<td>n.s.</td>
<td>2.097</td>
</tr>
<tr>
<td>CAR</td>
<td>1.217</td>
<td>.041</td>
<td>3.378</td>
</tr>
<tr>
<td>Cortisol AUC</td>
<td>.478</td>
<td>n.s.</td>
<td>1.612</td>
</tr>
<tr>
<td>Cortisol Slope</td>
<td>-.700</td>
<td>n.s.</td>
<td>.497</td>
</tr>
</tbody>
</table>

$\beta$ values indicate the strength of the relationship between the predictors and the outcome. $p$-values show the significance of these relationships. Exp($\beta$) represents the exponential of $\beta$, which can be interpreted as the multiplicative effect of the predictor on the outcome.

**Independent predictors** of new onset of mood disorders 1.5 years later:
- T1 Negative Emotion on Days of Cortisol Testing ($<.10$)
- T1 Episodic Stress (Life Events) ($<.05$)
- T1 Cortisol Awakening Response ($<.05$)

Also controlling for caffeine, nicotine, birth control use, race/ethnicity, SES, age, gender, % of time alone.
Figure 1. Baseline diurnal cortisol profiles of participants who do (dashed line) and do not (solid line) go on to develop an episode MDD over the following year.

High CAR = Risk Marker?

Adam et al. (In press), Psychoneuroendocrinology.
Survival Analysis: Cortisol Awakening Response and Unipolar Mood Disorder (New Onsets & Recurrences)

Adam, Vrshek-Schallhorn, in prep.
Key Points

- Multiple markers/indices of cortisol exist, defined by variations in the diurnal pattern.
- Different cortisol markers mean different things.
- In relation to MDD, my research suggests:
  - Flatter diurnal cortisol slope = state and scar.
  - Higher cortisol awakening responses = risk.
- HPA axis function dynamically changes with age, current stress, and illness stage.
- Need longitudinal, developmental data and a nuanced understanding of a system in order to understand the role of a particular marker/system in the etiology of disorder.
Multiple Influences on Cortisol Parameters

Current HPA Axis Functioning
(As Indexed by Cortisol Activity)

- Wakeup Level
- Bedtime Level
- Average Level
- Diurnal Slope
- Amplitude of Reactivity to Stressors
- Amplitude of Response to Awakening
- Efficiency of Negative Feedback and Stress Recovery
- Variability Within and Across Days

Historical Influences

- Prenatal and Early Postnatal Organizational Influences
- Childhood History of Stress, Support, and Trauma
- Physical, Mental Health, and Lifestyle History

Moderating Factors

- Temperament/Personality, Gender, and Genetic Variations
- Social Influences

Current Influences

- Recent/Immediate Emotional and Cognitive State
- Current Functioning of Related Physiological and Neurological Systems
- Current Psychopathology
- Current Physical Health and Lifestyle Factors
- Recent/Immediate Environmental Stresses and Supports

Adam et al., 2007
Thanks to...

Collaborators
- Sue Mineka, Rick Zinbarg, Michelle Craske
- Leah Doane, Amy DeSantis, Suzanne Vrshek-Schallhorn
- John Cacioppo, Louise Hawkley, Brigitte Kudielka

Participants
- Stress in the Working Family Study Participants
- Youth Emotion Project Participants
- CHASRS participants

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- National Institute on Aging
- National Institute of Child Health & Human Development
- National Academy of Education
- Alfred P. Sloan Foundation
- Spencer Foundation
- W.T. Grant Foundation
Three Level Model

Level 1:  \( \pi_0 + \pi_1 \times \text{Time Since Waking} + \pi_2 \times \text{Time Since Waking}^2 + \pi_3 \times \text{CAR} + e \)

Level 2:  \( \pi_0 \text{ to } \pi_3 = b_{i0} + b_{ij} \times \text{Prior Day Experience} + b_{ij} \times \text{Same Day Experiences} + b_{ij} \times \text{Day Level Controls} + r_{ij} \)

Level 3:  \( b_{i0} \text{ to } b_{ij} = g_{ij0} + g_{ijk} \times \text{Person Level Controls} + g_{ijk} \times \text{Average Experiences} + u_{ijk} \)
Diurnal Rhythm by Psychopathology
(Wave 1, Cross-sectional)

Cortisol (μg/dl) vs Time of Day

- No Psychopathology
- C. Affective
- C. Anxiety
- C. CoMorbid

* Significant difference
Cortisol Slopes with Psychopathology and Emotional Strain Variables (simple correlations)

<table>
<thead>
<tr>
<th></th>
<th>Correlations with Slopes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pearson $r$</td>
</tr>
<tr>
<td>Current Mood</td>
<td>.032</td>
</tr>
<tr>
<td>Current Anxious</td>
<td>.023</td>
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<tr>
<td>Current CoMorbid</td>
<td>.183*</td>
</tr>
<tr>
<td>ChronicRelStress</td>
<td>.156*</td>
</tr>
<tr>
<td>Episodic Stress</td>
<td>.151**</td>
</tr>
<tr>
<td>High Neuroticism</td>
<td>.174**</td>
</tr>
<tr>
<td>ESM Negative Emotion</td>
<td>.207**</td>
</tr>
</tbody>
</table>
Diurnal Rhythm by Cumulative Emotional Strain

![Graph showing cortisol levels across different times of day for different levels of cumulative emotional strain (No Strains, 1 Strain, 2 Strains, 3+ Strains).](image)

- *Dramatic flattening with 3 out of 4 of: high chronic relationship strain, high recent life stress, high neuroticism, and high state negative affect.*
**Figure 2.** Baseline diurnal cortisol profiles of Ps who do (dashed lines) and do not (solid line) develop an episode MDD over the following year, differentiating *initial onsets* of MDD (dark dashed line) and *recurrences* (light dashed line).
Current Depression if anything is associated with a low CAR
## Relationships among Strain and Psychopathology Variables

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
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<th>(6)</th>
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</thead>
<tbody>
<tr>
<td><strong>Mood</strong></td>
<td>1</td>
<td>-0.11</td>
<td>-0.091</td>
<td>0.165*</td>
<td>0.045</td>
<td>0.047</td>
<td>0.069</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>1</td>
<td>-0.112</td>
<td>0.127*</td>
<td>0.052</td>
<td>0.140*</td>
<td>0.163*</td>
<td></td>
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<tr>
<td><strong>CoMorbid</strong></td>
<td>1</td>
<td>0.299**</td>
<td>0.126*</td>
<td>0.342**</td>
<td>0.154*</td>
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<td></td>
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<tr>
<td><strong>Chronic</strong></td>
<td>1</td>
<td>0.215**</td>
<td>0.220*</td>
<td>0.155*</td>
<td></td>
<td></td>
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<tr>
<td><strong>Episodic</strong></td>
<td>1</td>
<td>0.221**</td>
<td>0.09</td>
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<tr>
<td><strong>ESM Negative</strong></td>
<td>1</td>
<td>0.277**</td>
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<tr>
<td><strong>Neuroticism</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>1</td>
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</tbody>
</table>
## Intercorrelations Among Cortisol Indices

<table>
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<tr>
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<tbody>
<tr>
<td>CAR</td>
<td>1</td>
<td>.298**</td>
<td>.280**</td>
</tr>
<tr>
<td>AUC</td>
<td>.298**</td>
<td>1</td>
<td>.413**</td>
</tr>
<tr>
<td>Slope</td>
<td>.280**</td>
<td>.413**</td>
<td>1</td>
</tr>
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</table>
### Cortisol Parameters and Cardiovascular Risk

<table>
<thead>
<tr>
<th></th>
<th>Waist/Hip Ratio</th>
<th>HDL Cholesterol</th>
<th>Total/HDL Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Cortisol Awakening Response</td>
<td>.29**</td>
<td>-.25*</td>
<td>.25*</td>
</tr>
<tr>
<td>Flatter Cortisol Slope</td>
<td>.28*</td>
<td>-.24*</td>
<td>.25*</td>
</tr>
</tbody>
</table>

Controlling for age, SES, smoking, alcohol, time of awakening

Steptoe et al., 2004
Central Adiposity and Cortisol Responses to Awakening
Fig. 2. Kaplan-Meier survival curves for patients split into two equal groups at the median diurnal cortisol slope (~0.091 log [µg/dL] per hour). This grouping was performed only to illustrate survival curves representing patients with relatively steep versus flat cortisol slopes. The definitive survival analysis was conducted on the entire sample using the continuous variables of cortisol slope and survival time in a Cox regression. Patients with relatively flat cortisol slopes experienced shorter subsequent survival (Cox proportional hazards, two-tailed $P = .0036$). Among the patients split at the median cortisol slope, 77% of those with flat rhythms died, after surviving an average of 3.2 years (broken line). In contrast, 60% of the patients with relatively steep rhythms died, but they survived more than 1 year longer on average, with an average survival of 4.5 years (solid line). Survival plots of these groups diverged significantly (log-rank, two-tailed $P = .016$). Patients still living at the time of analysis are indicated by black vertical slash marks. The numbers of living patients at each year mark are listed for the “flat-slope” and “steep-slope” groups whose survival curves are shown in the figure.