Boys’ middle-childhood testosterone-to-cortisol responsivity ratio and externalizing & substance use problems in adolescence and early adulthood

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Testosterone-Cortisol Ratio

- High T / Low C imbalance linked to aggression/externalizing
  Terberg et al., 2009; Montoya et al., 2012; van Honk et al., 2010

- High basal T / Low cortisol responsivity
  - Higher externalizing in adults
  Glenn et al., 2011

- Stress and sex hormones inversely associated in adults
  Tong et al., 2013

- But: adolescence = marked activation of both axes
  - Developmental switch-point in late adolescence
  Marceau et al., 2015; Shirtcliff et al., 2015; Ruttle et al., 2015

- Question: Does the pattern found in Glenn et al., (2011) replicate in adolescence?
Gaps in the Literature

Shared Genetic influences

- **HPA pathway genes**
  - Key regulators of hormone production
  - Shown to be associated with externalizing and SU
  - May in part mediate hormone-behavior associations

Developmental Transition to Substance Use

- **#1 Predictor of SU: earlier externalizing problems**
  
  Colder et al., 2013; Disney et al., 1999; Helstrom et al., 2004; Molina & Pelham, 2003; Wilens et al., 2011

  - Shared Genetic Influences
    Hicks et al., 2011; Iacono et al., 1999

  - Shared theoretical rationale for role of hormonal milieu
Questions:

1. Does the T/C responsivity ratio finding from Glenn et al., (2011) replicate in adolescence?

2. Is T/C responsivity ratio implicated in transitions from externalizing through SU to SUD severity in adulthood?

3. Do these patterns survive after controlling for relevant genetic influences, or are associations genetically mediated?

Do these patterns vary for youth at high vs. low risk for SU?
CEDAR: Participants

- Center for Education and Drug Abuse Research
- N ~ 775, 71% male
- High Risk Group: n = 425 (106 with genetic data)
  - Biological children of men with a SU (N = 344) or Psychiatric (N = 81) disorder
- Control Group: n = 350 (131 with genetic data)
  - Biological children of men with no disorder

<table>
<thead>
<tr>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
<th>Wave 5</th>
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</thead>
<tbody>
<tr>
<td>Age 10-12</td>
<td>Age 12-14</td>
<td>Age 16</td>
<td>Age 19</td>
<td>Age 22</td>
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<tr>
<td>N = 695</td>
<td>N = 586</td>
<td>N = 627</td>
<td>N = 583</td>
<td>N = 437</td>
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</tbody>
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http://www.pitt.edu/~cedar/design.html
Measures: Hormones

- Basal Testosterone
  - Blood collected at 8:30am
  - Amersham’s testosterone/DHT RIA kit

- Cortisol Responsivity
  - Saliva collected prior to (9:00am) and after (10:15am) auditory evoked ERP
  - DELPHIA

- Data prep for both hormones:
  - Outliers past 3SDs were windorized
  - Scores log-transformed

- Cortisol responsivity = post - pre
  Increase in cortisol: 26% W1, 27% W3
Measures: Ratios

- T/C responsivity ratios
  - Standardized T and C responsivity scores to Tscores
    - M = 50; SD = 10
    - Ratio = T/C responsivity

- Calculated at W1 and W3
  - Only W1 used moving forward because of low N at W3

Generally, balanced T/C levels

Not stable over years

<table>
<thead>
<tr>
<th></th>
<th>W1 (N = 439 full sample)</th>
<th>W3 (N = 154 full sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Sample</td>
<td>M = 1.01 (SD = .28); 44% &gt;1</td>
<td>M = 0.99 (SD = .24); 47% &gt;1</td>
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<td></td>
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<tr>
<td></td>
<td>r = .11,  p = .25 (N = 116)</td>
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<tr>
<td>High Risk</td>
<td>M = 0.98 (SD = .27); 40% &gt;1</td>
<td>M = 1.02 (SD = .26); 60% &gt;1</td>
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<tr>
<td></td>
<td>r = .23,  p = .11 (N = 52)</td>
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</tr>
<tr>
<td>Low Risk</td>
<td>M = 1.05 (SD = .28); 47% &gt;1</td>
<td>M = 0.96 (SD = .22); 40% &gt;1</td>
</tr>
<tr>
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<td>r = .02,  p = .89 (N = 64)</td>
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</table>
Measures: Outcomes

■ Externalizing problems
  - *Multi-measure Multi-rater composite*
    ■ Tarter Childhood History Questionnaire, CBCL/TRF, Diagnostic instruments, Dysregulation inventory, Conners
    ■ Child, Mother, Teacher
    - Waves 1 and 2

■ Substance Use Severity
  - *IRT from diagnostic instruments*
  - Waves 3 and 4

■ Substance Use Disorder Severity
  - *IRT from diagnostic instruments*
  - Wave 5

[http://www.pitt.edu/~cedar/TLldocument.html](http://www.pitt.edu/~cedar/TLldocument.html)

Kirschi et al., 2002; 2006
Measures: Genes

- Cortisol-related genes
  - Identified ~200 genes from Biosystems databases & literature
  - Cross-referenced with available SNPs from candidate genes in CEDAR
  - Applied standard QC, pruned for LD > .7
  - $N_{snp} = 210$ from 23 genes
Analytic Strategy

1. T/C ratio – outcome associations (SAS: proc corr)
2. SEM in full sample without genetic influences (R:lavaan)
   2(b) examine group differences
3. SEM in full sample with genetic influences
   3(b) examine group differences

Age 10-12 Externalizing → Age 12-14 Externalizing → Age 16 SU severity → Age 19 SU severity → Age 22 SUD severity

Age 10-12 T/C ratio → Polygenic Score on T/C ratio
Results

1. T/C ratio – outcome associations

Note: All outcomes inter-correlated, except control Age 12-14 Externalizing with Age 19 SU severity.

Gray lines indicate tested associations that were not significant. Significant (p > .05) Pearson’s r presented.

Lower T relative to higher C responsivity associated with SUD problems.
1. T/C ratio – outcome associations

- Age 10-12 T/C ratio
- Age 10-12 Externalizing
- Age 12-14 Externalizing
- Age 16 SU severity
- Age 19 SU severity
- Age 22 SUD severity

Lower T relative to higher C responsivity associated with Ext in controls & SUD problems in both groups.

Note: All outcomes inter-correlated, except control Age 12-14 Externalizing with Age 19 SU severity.
Results

2. SEM in full sample without genetic influences

Gray lines indicate tested paths that were not significant. Black thin lines indicate trend-level paths ($p < .10$). Black bold lines indicate significant paths ($p < .05$).

Lower T relative to higher C responsivity associated with SUD problems after accounting for developmental behavioral trajectories.
2. SEM in full sample without genetic influences: by group

No T/C ratio effects were significant.
Implications

- Opposite T/C ratio effect than that found in adults
- In adults, associations of T/C ratio with psychopathy were driven by men for whom the T/C ratio was driven by T

<table>
<thead>
<tr>
<th>W1 Ratio:</th>
<th>(&lt; 1) Higher C relative to T</th>
<th>(&gt;1) Higher T relative to C</th>
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<tbody>
<tr>
<td>Testosterone</td>
<td></td>
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<tr>
<td>Below average</td>
<td>49% (52%, 47%)</td>
<td>13% (12%, 14%)</td>
</tr>
<tr>
<td>Above average</td>
<td>7% (8%, 5%)</td>
<td>31% (28%, 34%)</td>
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<tr>
<td>Cortisol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below average</td>
<td>20% (20%, 21%)</td>
<td>27% (23%, 32%)</td>
</tr>
<tr>
<td>Above average</td>
<td>36% (41%, 32%)</td>
<td>16% (17%, 16%)</td>
</tr>
</tbody>
</table>

- T/C ratios less important than developmental trajectories
- T/C ratios more important for youth without elevated risk
Results

3. SEM in full sample with genetic influences

Polygenic score findings based on 15% of total N, ~97 contribute to the significant association depicted.
Results

3. SEM in full sample with genetic influences: by group

Polygenic score findings based on 15% of total N, ~ 34-66 contribute to the significant associations depicted.
Limitations

■ Genetic component
  - Only ~30% of sample had genetic data
  - Only ~15% of data available in SEM

■ Few girls, too small of sample size to test for gender differences and group differences
  - Results with only boys were very similar

■ Aggression vs. rule breaking
  - $T$ and $C$ independently related to each and substance use
  - $T/C$ ratio specific to aggression?
Conclusions

- T/C responsivity ratios are different in adolescence than adulthood, and differentially associated with behavior

- T/C responsivity ratios in adolescence predict SUD problems at age 22 after accounting for developmental behavioral trajectories
  - *Though a small effect*

- Very preliminary evidence that genetic influences could mediate associations, with many caveats
Acknowledgements

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