Developmental Twin Studies of Relations Between Substance Use and ADHD

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  - M. Rietveld, Ph.D.
  - T. van Beijsterveldt, Ph.D.
  - Eske Derks

- Vermont
  - Cathy Stanger, Ph.D
  - David Rettew, M.D.
  - Rob Althoff, Ph.D., M.D.
  - Bill Copeland, Ph.D.
Collaborators - Away:

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- Andrew Heath, D. Phil., Washington University
Support:

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- Spinoza and NWO 575-25-006 grants to D. Boomsma.
Outline:

- Introduction
- The Child Behavior Checklist (CBCL).
- Multi-Informant Cross-Sectional Data on AP, AGG, and RB.
- Longitudinal Data on AP and AGG.
- Comorbidity Data AGG/RB.
- Maternal Smoking Data and AP and AGG.
- Longitudinal Latent Class Approaches on ADHD Data.
- Discussion.
Maternal Smoking increases the risk for child psychopathology (ADHD, ODD, RB (DB)).

Child Psychopathology increases risk for Alcohol and cigarette use.

But in which specific children?

What about persistence?
### Netherlands Twin Register

**25,000 twin pairs registered at birth, born after 1986**

<table>
<thead>
<tr>
<th>Questionnaire variables</th>
<th>2, 3, 5, 7, 10, 12</th>
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<tbody>
<tr>
<td>Zygosity, health and growth</td>
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<td>SES</td>
<td>3, 7, 10, 12</td>
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<td>Problem behavior</td>
<td>3, 5, 7, 10, 12</td>
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<td>CBCL (Devereux at 5)</td>
<td>3, 5, 7, 10, 12</td>
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<tr>
<td>TRF</td>
<td>7, 10, 12</td>
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<tr>
<td>YSR</td>
<td>12</td>
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<tr>
<td>Conners ADHD-I and ODD data</td>
<td>7, 10, and 12</td>
</tr>
</tbody>
</table>
What is the Child Behavior Checklist?

- 118 items of common behavior
- Reported on by mothers, fathers, teachers (Teacher Report Form), and children (Youth Self Report).
- Scored 0,1,2.
- Factor analyzed
- 8 Syndromes (AP, AGG, A/D)
CBCL Clinical Scales

Mean

Delinquent Behavior  Aggressive Behavior  Withdrawn  Somatic Complaints  Anxious Depressed  Social Problems  Thought Problems  Attention Problems

CBCL – Juvenile Bipolar Phenotype
ADHD
Control

Hudziak/Boomsma/Todd APA
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CBCL-DSM Predictive Relations

- AP - ADHD (93%)
- AGG - ODD/CD, (95%)
- AGG + DB - CD (92%)

Biederman et al (1992), Steingard et Al (1994), and Chen et al. (1994), have all published similar results.
Univariate AGG, AxD, & AP

Data: CBCL. N Pairs: 84 MZM; 118 DZM; 68 MZF; 98 DZF
### Univariate AGG, AxD, & AP

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<th>df</th>
<th>p</th>
<th>a²</th>
<th>e²</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AP:</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>3</td>
<td>.73</td>
<td>.77</td>
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<td>F</td>
<td>2.21</td>
<td>3</td>
<td>.53</td>
<td>.70</td>
<td>.30</td>
<td>-.0</td>
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<tr>
<td>AxD:</td>
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<tr>
<td>M</td>
<td>2.17</td>
<td>4</td>
<td>.70</td>
<td>.65</td>
<td>.35</td>
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<td>4</td>
<td>.82</td>
<td>.61</td>
<td>.39</td>
<td>*</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>6.34</td>
<td>3</td>
<td>.10</td>
<td>.69</td>
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<td>.0</td>
</tr>
<tr>
<td>F</td>
<td>5.97</td>
<td>4</td>
<td>.20</td>
<td>.70</td>
<td>.30</td>
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</tbody>
</table>

* ci’s encompass 0

Data: CBCL. N Pairs: 84 MZM; 118 DZM; 68 MZF; 98 DZF
Developmentally Sensitive Analysis

Mom

AP

Age 3
Developmentally Sensitive Analysis

Mom

AP

Age 3

Mom

AP

Age 7
Developmentally Sensitive Analysis

Mom

Age 3

AP

Mom

Age 7

AP
Developmentally Sensitive Analysis

Mom

AP
Age 3

Mom

AP
Age 7

Mom

AP
Age 10
Developmentally Sensitive Analysis

Mom

AP
Age 3

AP
Age 7

AP
Age 10
Developmentally Sensitive Analysis

Mom

AP
Age 3

AP
Age 7

AP
Age 10

AP
Age 12
Heritability of attention problems in children: Cross sectional results from a study of twins, age 3-12 years.

CBCL/4-18 for 7-, 10-, and 12-year-olds

Attention problems [AP]

1. Acts too young for his/her age
2. Can’t concentrate, can’t pay attention for long
3. Can’t sit still, restless, or overactive
4. Confused or seems to be in a fog
5. Daydreams or gets lost in his/her thoughts

41. Impulsive or acts without thinking
45. Nervous or tense
46. Nervous movements or twitching
61. Poor school work
62. Clumsy or poorly coordinated
80. Stares blankly
Dutch twin correlations: Mother ratings for overactive behavior (3 yr), 5-item attention (5 yr), CBCL attention problems (7, 10, 12 yr); total N = 3835 (3), 6660 (5), 3427 (7), 2504 (10) and 1307 (12) pairs.
Longitudinal of AP

- Broad heritability of AP are estimated at nearly 75%, at each age. The results indicated revealed less stability at age 3 to AP at age 7 (r = .40), compared to the stability from AP at age 7 and beyond (r = .70). Genetic effects were found to explain between 70% of the variance across development.
- AP is found highly heritable at all ages in both genders. The same set of genes appears to be expressed in boys and girls.
- The genetic and environmental contributions remain stable across the ages studied. Stability AP is accounted for by genetic influences.
- Children who do not display AP at a given age are unlikely to develop these problems at a subsequent age.
Individual Differences in Aggression: Genetic Analyses by age, gender, and informant in 3-, 7-, and 10-year-old Dutch Twins.


- In Press, Behavioral Genetics, 2003
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
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<tbody>
<tr>
<td>Argues</td>
<td>Attacks</td>
</tr>
<tr>
<td>Bragging</td>
<td>Screams a lot</td>
</tr>
<tr>
<td>Mean to others</td>
<td>Showing off, clowning</td>
</tr>
<tr>
<td>Demands attention</td>
<td>Stubborn</td>
</tr>
<tr>
<td>Destroys own things</td>
<td>Mood changes</td>
</tr>
<tr>
<td>Destroys others’ things</td>
<td>Talks too much</td>
</tr>
<tr>
<td>Disobedient at home</td>
<td>Teases a lot</td>
</tr>
<tr>
<td>Disobedient at school</td>
<td>Temper</td>
</tr>
<tr>
<td>Jealous</td>
<td>Threatens others</td>
</tr>
<tr>
<td>Gets in fight</td>
<td>Loud</td>
</tr>
</tbody>
</table>
Results Cross-Sectional AGG

- Differences in raw scores across gender were found, with boys being rated as more aggressive than girls by all informants. Mothers reported more symptoms than fathers, who reported more symptoms than teachers. **Evidence for moderate to high genetic influence (51% to 72%) was seen for AGG by all three informants at all ages** with only small sex differences in heritability estimates, except for teacher reports on girls.

- Teachers on girls, yields evidence of genetic dominance.

- Best fitting models for AGG by parent reports also included a small contribution of common environment. The largest sex differences in heritabilities were seen at age 10. Contributions of common (13% to 27%) and unique (16-31%) environment were small to moderate. There was some evidence of genetic dominance by teacher report for 10-year-old girls.

- **Although M, F, and T reports only correlated ~.38%, all informants identify genetic influences exceeding .68%.**
Causes of stability of aggression from early childhood to adolescence: A longitudinal genetic analysis in Dutch twins

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1Department of Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands.
2Department of Psychiatry and Medicine (Division of Human Genetics), Center for Children, Youth and Families, and University of Vermont, College of Medicine, Burlington, USA

Behavior Changes over Time:

Mean Aggressive Syndrome
Averaged Across Cohorts

Stability:

- AGG showed moderate to high stability during childhood. The stability coefficients ranged from 0.41 to 0.77 across varying intervals. Averaged across boys and girls, genetic factors accounted for approximately 65% of the total stability.

- On average, 6-8% of the children meet clinical severity criteria.

- Longitudinal genetic analysis indicated a simplex model for genetic effects, which suggest a dynamic development process consisting of transmission of existing genetic effects interacting with new genetic influences. In conclusion, these data support the idea that both genetic and environmental influences play a role in the stability of AGG from age 3 to 12.
Delinquent Behavior (Now Rule Breaking)

- Rule Breaking syndrome behaviors are as they sound. These are kids who break rules. Operationally are similar to T Moffitt’s adolescent limited conduct disorder type. Indeed, RB is predictive of DSM CD diagnosis.

- Rule Breaking Behavior (formally, delinquent behavior) has been shown to be most predictive of adolescent substance use. Stanger et al, 2000.
Mean Delinquent Syndrome
Averaged Across Cohorts

### Results for DB/RB at Age 7, 10, & 12

<table>
<thead>
<tr>
<th>Age</th>
<th>MOM</th>
<th>DAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>.50 (.42-.56)</td>
<td>.30 (.25-.37)</td>
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<tr>
<td>12</td>
<td>.60 (.46-.71)</td>
<td>.23 (.13-.36)</td>
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<tr>
<td>7</td>
<td>.34 (.33-.43)</td>
<td>.44 (.36-.51)</td>
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<tr>
<td>12</td>
<td>.23 (.11-.33)</td>
<td>.52 (.42-.62)</td>
</tr>
<tr>
<td>7</td>
<td>.36 (.30-.54)</td>
<td>.39 (.32-.54)</td>
</tr>
</tbody>
</table>
Co-occurrence of Aggressive Behavior and Rule-Breaking Behavior at Age 12: Multi-Rater Analyses


In press, Behavioral Genetics, 2003
Bivariate AGG, and RB

Genetics of Comorbidity between AGG and RB (ODD and CD for DSM Comparison).

- Genetic influences account for 79% and 69% of the individual differences in RB and AGG behavior (defined as AGG and RB on which both parents do agree) in boys. In girls 56% and 72% of the variance in RB and AGG are accounted for by genetic factors. **Shared environmental influences are significant for RB in girls only, explaining 23% of the total variance.**

- Eighty percent of the covariance between AGG and RB, similarly assessed by both parents, can be explained by genetic influences. So, co-occurrence in AGG and RB is mainly caused by a common set of genes.

- **Children who suffer AGG or RB in the clinical range are at equal risk to have the comorbid disorder as well. In our sample 50.0% to 63.9% of the children who are deviant on AGG are also deviant on RB and vice versa.**
Maternal Risk Factors

- Again, for this meeting, our group ran analyses of maternal smoking behavior on measures of AP and AGG at each age.
- Smoking behavior for this work was obtained from parental interviews when the twins were born.
- Smoking data are:
  - Never smoked during pregnancy.
  - Did smoke
    - Less than 10 a day.
    - More than 10 a day.
Maternal smoking during pregnancy and Aggressive Behavior (CBCL) at age 7
Maternal smoking during pregnancy and Aggressive Behavior (CBCL) at age 10

Mean score for AGG

SMOKING BEHAVIOR MOTHER
(during pregnancy)
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Maternal smoking during pregnancy and Attention Problems (CBCL) at age 7

Mean score for AP

SMOKING BEHAVIOR MOTHER (during pregnancy)

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Maternal smoking during pregnancy and Attention Problems (CBCL) at age 10

Mean score for AP

SMOKING BEHAVIOR MOTHER
(during pregnancy)
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Are longitudinal twin studies useful for the study of substance use?

• We think so.
• Our twins are approaching peak age of initiation and regular use.
• Using persistent phenotypes may allow us to develop a strategy to identify not only those who are at greater risk to experiment, but also those who are at greater risk to abuse.
Discussion of DSM ADHD Studies

• These slides are provided by R. Todd et al.
• They focus on many analytic approaches we have used to test the relations between genetic and environmental factors on risk for ADHD and SUD.
Latent Class Analysis And Heritability of ADHD
Fig. 1 Latent class analysis of DSM-IV attention-deficit/hyperactivity disorder.

Latent Class Analysis of Co-morbidity: ADHD, MDD, ODD and Anxiety
MOAFTS: N=2,904
Inattentive Classes

- ADHD-IA+ODD (5.3)
- ADHD-IA (8.9)
- Base Rate
MOAFTS (N=2,904)
Combined, Mild Hyperactive-Impulsive Classes
Inattentive Combined Inattentive Combined DSM-IV Latent Class

Odds Ratio

All values are adjusted odds ratios from multivariate logistic regression. Huber-White Robust estimators were used to correct for clustered data (i.e., twins). Covariates included sex, age, race, zygosity, smoking, marijuana usage, major depression, oppositional defiant disorder and conduct disorder. ns = not significant.

p = 0.03

All values are adjusted odds ratios from multivariate logistic regression. Huber-White Robust estimators were used to correct for clustered data (i.e., twins). Covariates included sex, age, race, zygosity, alcohol abuse, marijuana usage, major depression, oppositional defiant disorder and conduct disorder. ns = not significant.
Kaplan-Meier Estimate of Survival Curves for Missouri Adolescents Aged 10-18 Years Stratified by Latent-Class Severe Combined Subtype

- Age at First Drink
  - Few
  - S-Comb
  - p=.0259

- Age at First Cigarette
  - Few
  - S-Comb
  - p=.0007
Kaplan-Meier Estimate of Survival Curves for Missouri Adolescents Aged 10-18 Years
Stratified by Latent-Class Severe Inattention Subtype

- **Age at First Drink**
  - Few
  - S-INATTN
  - $p = 0.0003$

- **Age at First Cigarette**
  - Few
  - S-INATTN
  - $p = 0.0383$
Summary:

- We have identified children with highly deviant, persistent, and comorbid forms of AGG/RB and AP.
- We have used LCA and other novel approaches to the relations between DSM ADHD and SUD.
- A longitudinal twin approach may allow us to test these high risk, persistent phenotypes for initiation, abuse, and dependence studies.
- Use during pregnancy can be used as a covariate.
- Extended the twin model to a family design may then provide a model for considering both genetic and environmental contributions to initiation and persistence.
The End.

Thank You.