Genetic Epidemiological Perspectives on Alcohol Use and Dependence

Society for Neuroscience:

Henri Begleiter Symposium

11/2/07

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Outline of Talk

1. Examine the specificity of genetic risk factors for alcohol abuse/dependence.
2. Explore the changing role of shared environment and genes in influencing alcohol intake over development.
3. Examine the sources of individual differences over development in self-ratings of alcohol availability.

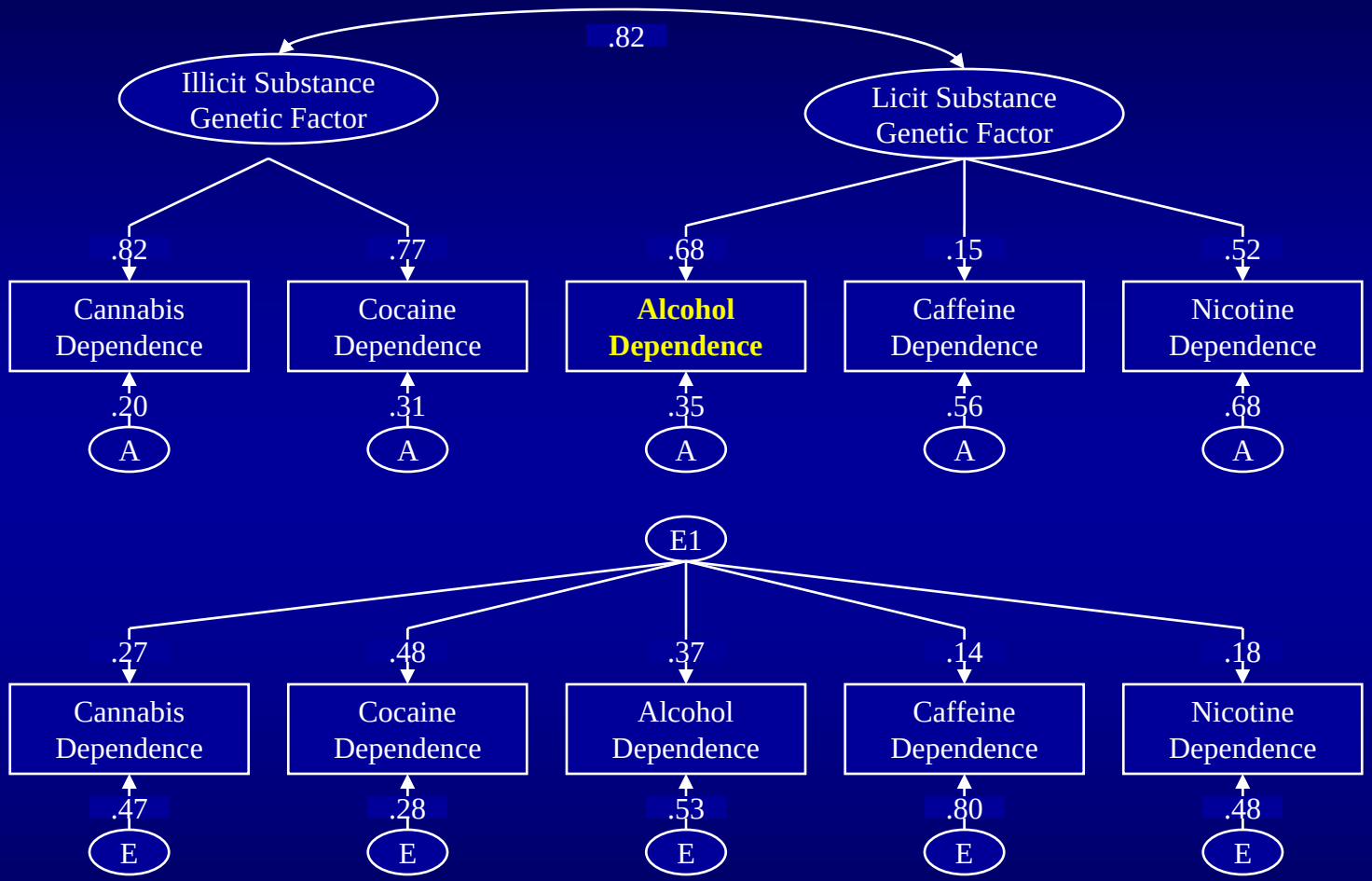
Outline of Talk

4. Determine the role of genetic factors in determining the social environment.

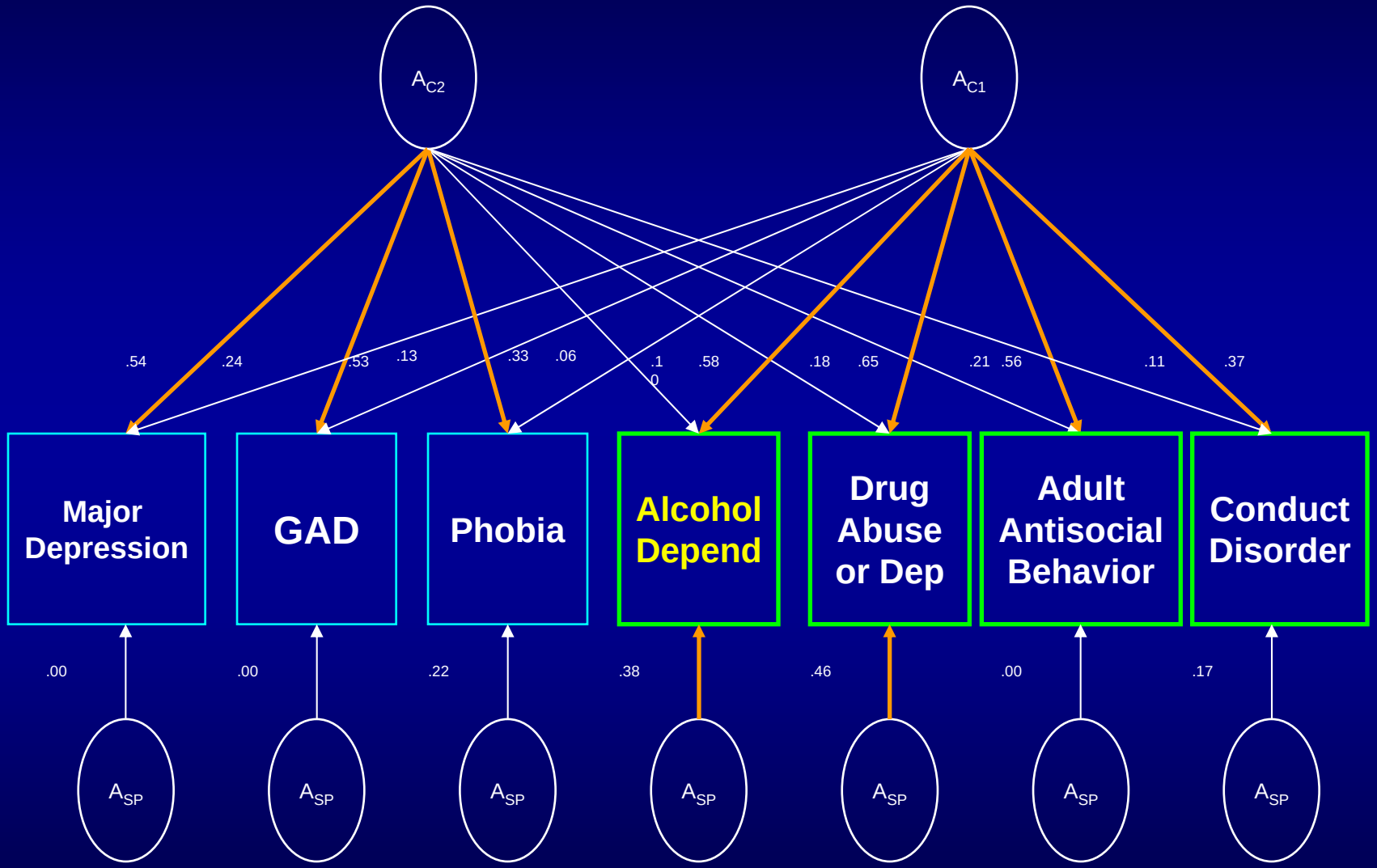
5. Use genetic epidemiological methods to disentangle the causal inter-relationships between person and peer group deviance.

Specifity of Genetic Risk Factors for Alcohol Abuse/Dependence

- Sample -- over 4,500 members of male and female twin pairs from the Virginia Twin Registry, all personally interviewed.
- First analysis -- 7 common psychiatric and substance use disorders assessed at personal interview.
- Second analysis – Abuse/dependence of 5 psychoactive substances
  - 3 licit: caffeine, nicotine and alcohol
  - 2 illicit substances: cannabis and cocaine.


.82
Illicit Substance Genetic Factor
Licit Substance Genetic Factor
.82
.77
.68
.15
.52
Cannabis Dependence
Cocaine Dependence
Alcohol Dependence
Caffeine Dependence
Nicotine Dependence
.20
.31
.35
.56
.68
A
A
A
A
A
E1
.27
.48
.37
.14
.18
Cannabis Dependence
Cocaine Dependence
Alcohol Dependence
Caffeine Dependence
Nicotine Dependence
.47
.28
.53
.80
.48
E
E
E
E
E

Genetic Sources of Comorbidity in Common Psychiatric And Drug Use Disorders



DEP = dependence
GAD = generalized anxiety disorder

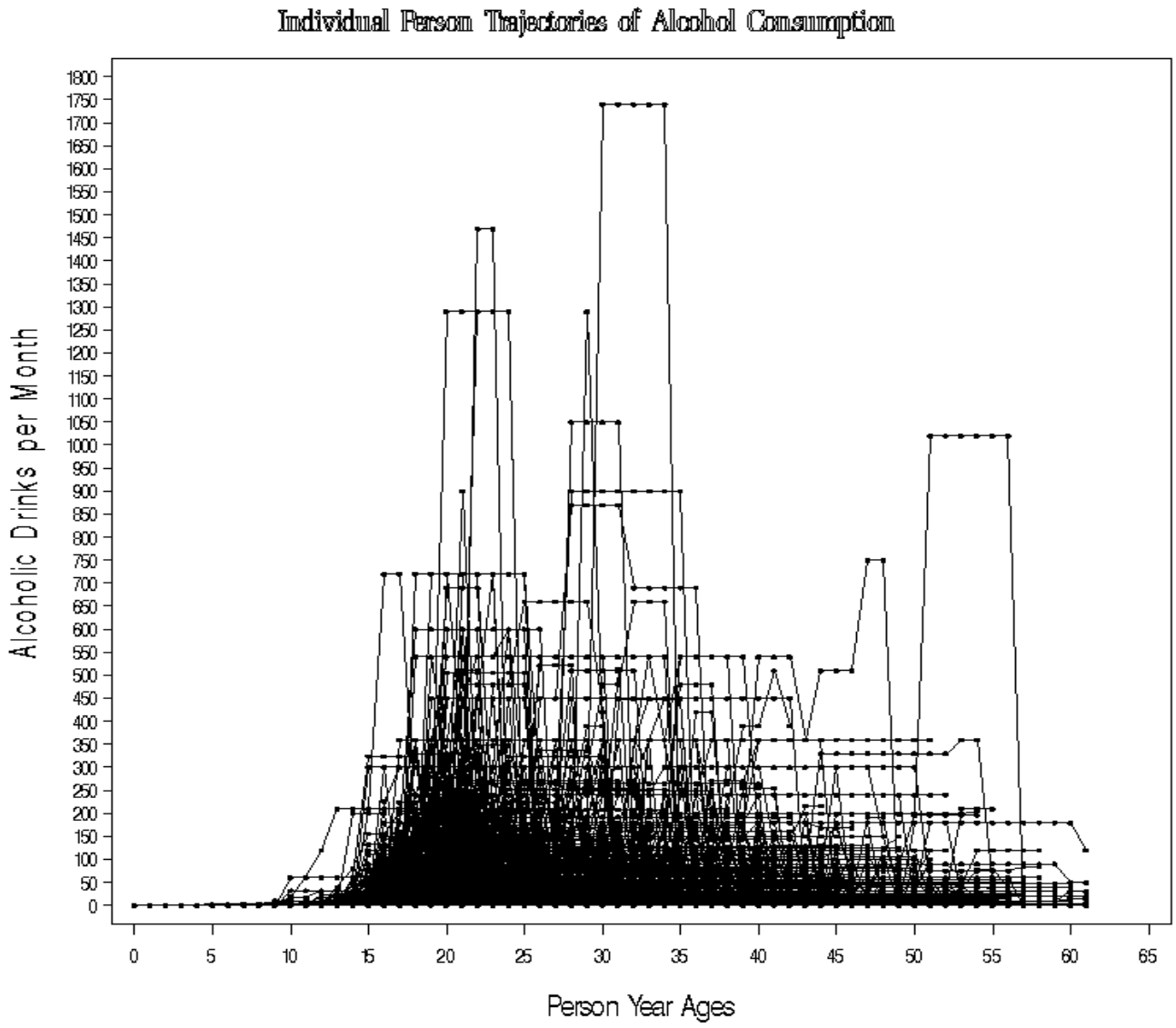
Individual Differences in Psychoactive Substance Use Across the LifeSpan

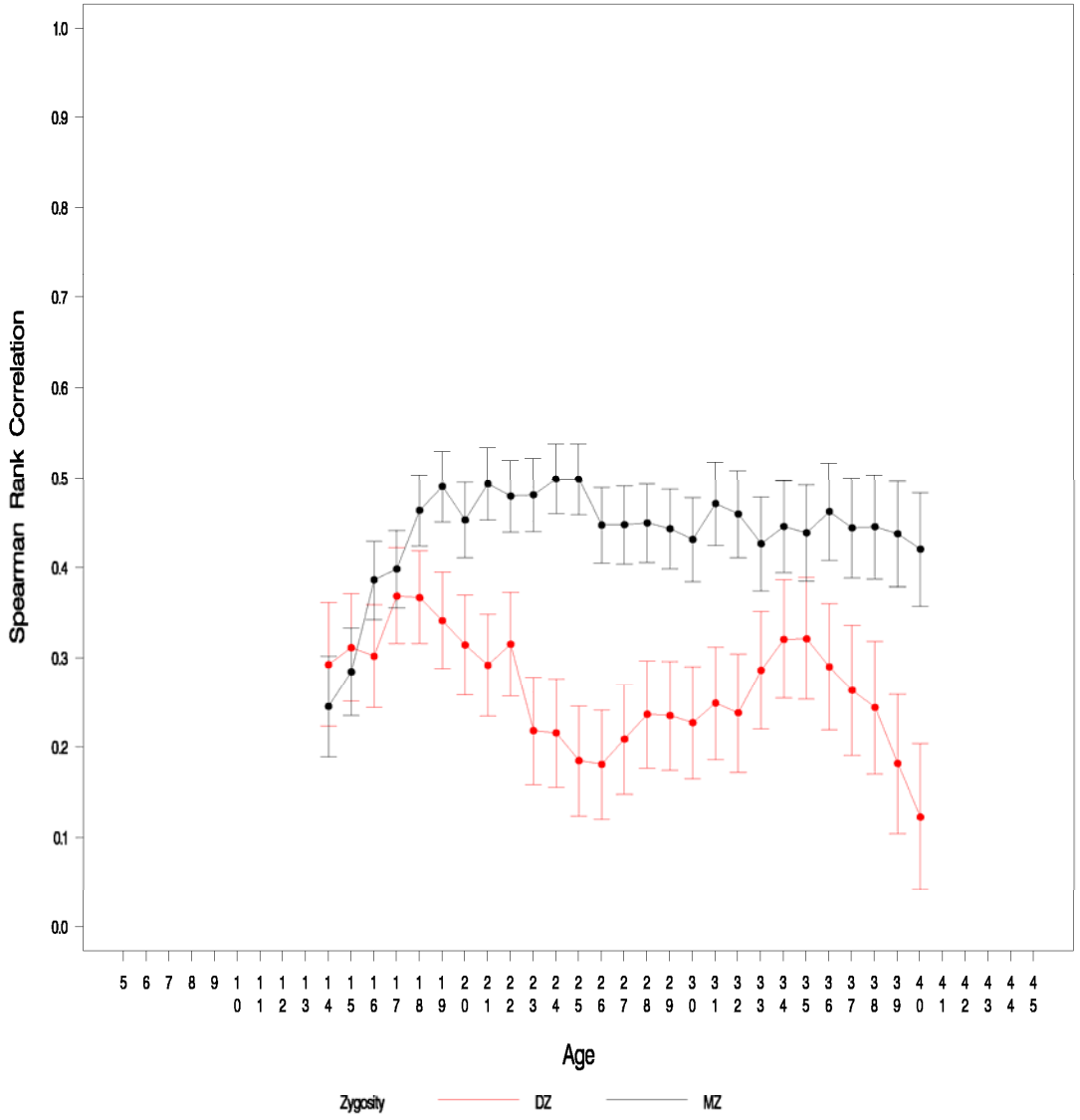
- Use of calendar data from this same sample.
- Useful data on nicotine, caffeine, alcohol and cannabis. Will only look at alcohol use here.
- Look at univariate results across years of age

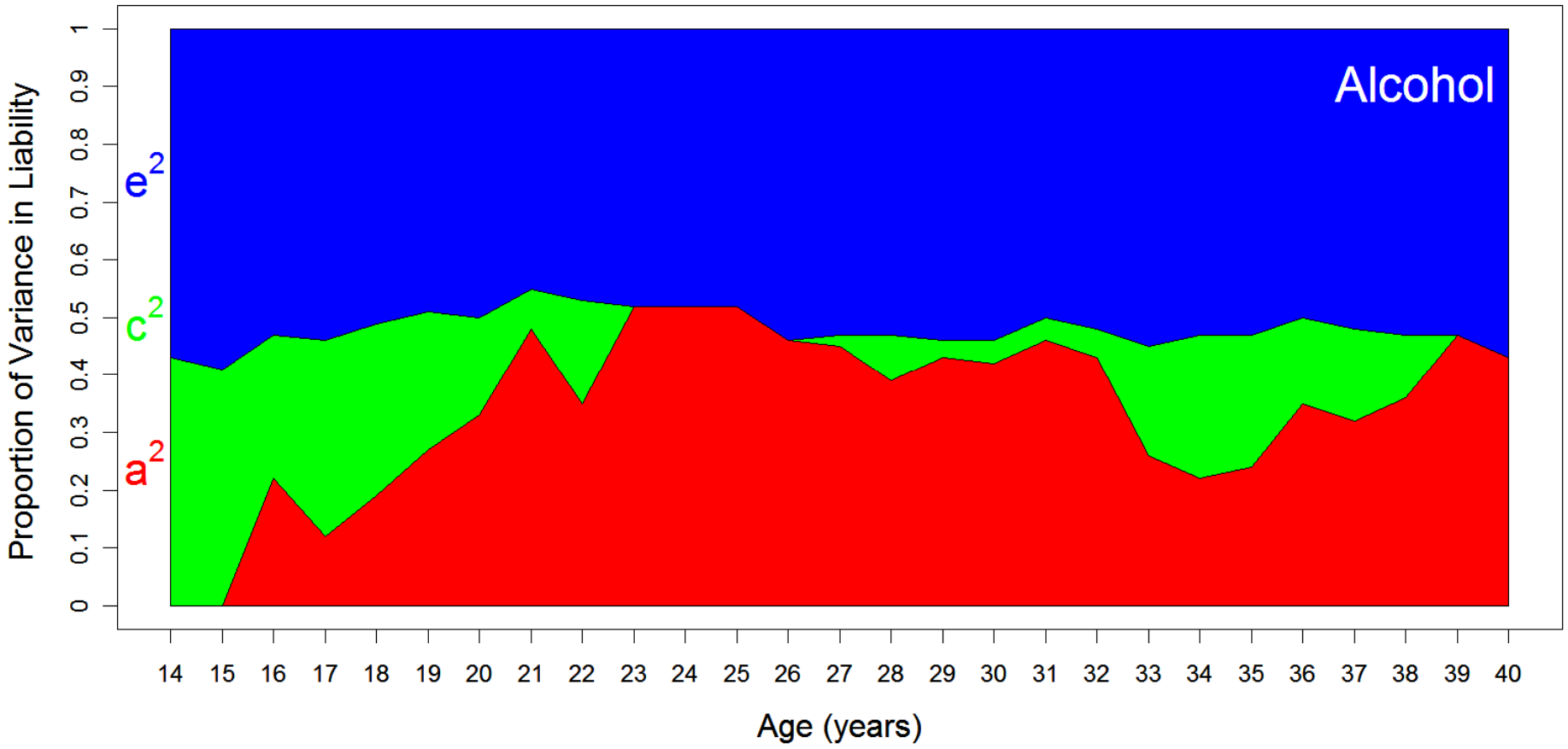
Sources of Individual Differences in Self-Report Alcohol Availability

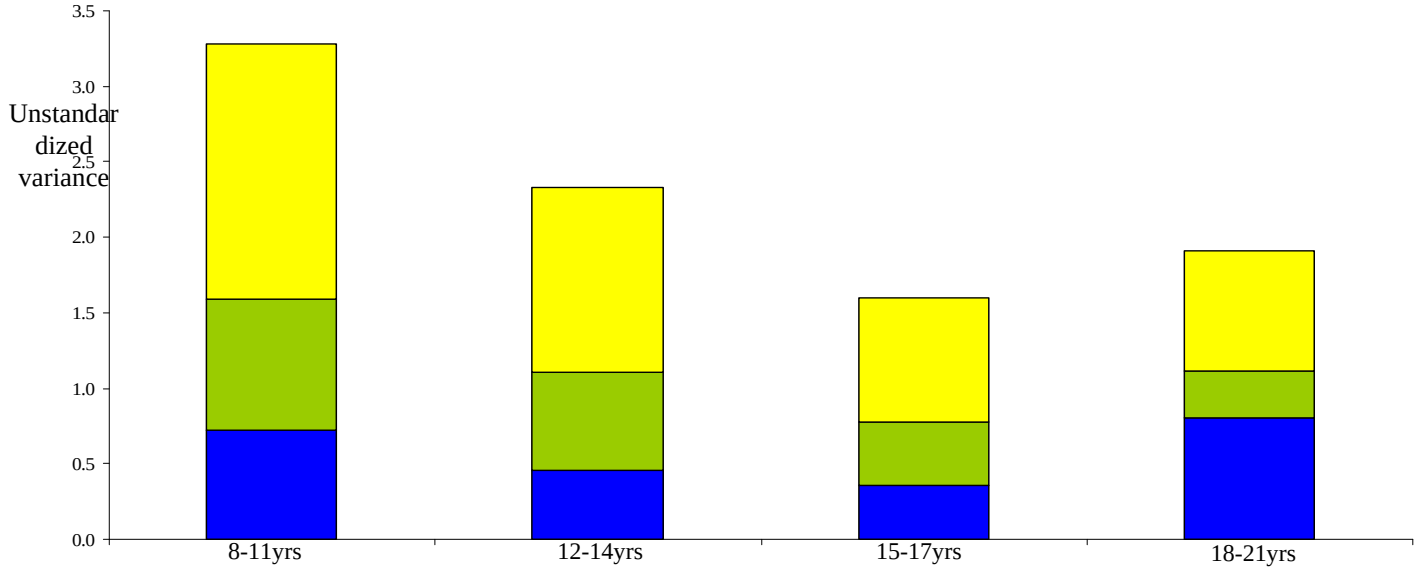
- Measures of average alcohol intake retrospectively reported by the life history method for each year up to their present age.
- ~750 male-male twin pairs.
- From the third interview wave with male-male twins, completed in 1998-2004 by 1796 male twins (75%) who had participated in the second interview. Subjects were 24-62 years old (mean age = 40.3 years, SD = 9.0).

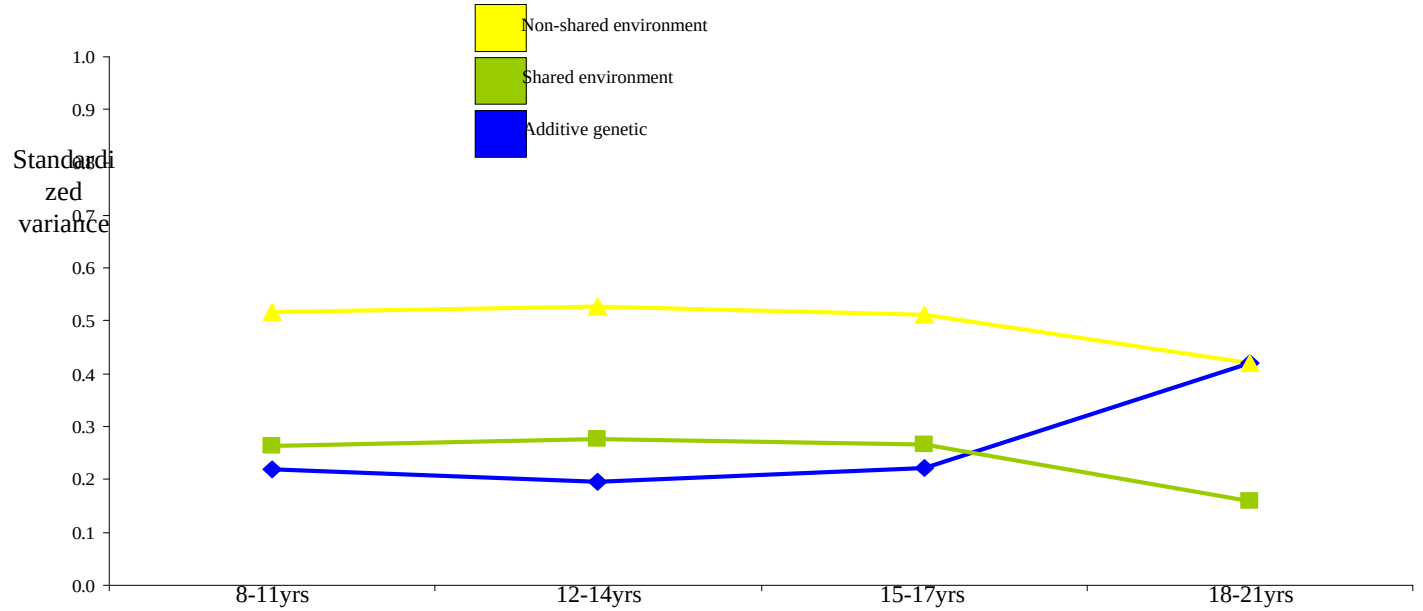
ALCOHOL


Individual Person Trajectories of Alcohol Consumption
Alcoholic Drinks per Month
1800
1750
1700
1650
1600
1550
1500
1450
1400
1350
1300
1250
1200
1150
1100
1050
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
Person Year Ages


Spearman Rank Correlation
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
Age
Zygosity
DZ
MZ


Alcohol
e^2
c^2
a^2
Proportion of Variance in Liability
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Age (years)


Unstandardized variance
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
8-11yrs
12-14yrs
15-17yrs
18-21yrs


Non-shared environment
Shared environment
Additive genetic
Standardized variance
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
8-11yrs
12-14yrs
15-17yrs
18-21yrs

Models of Development

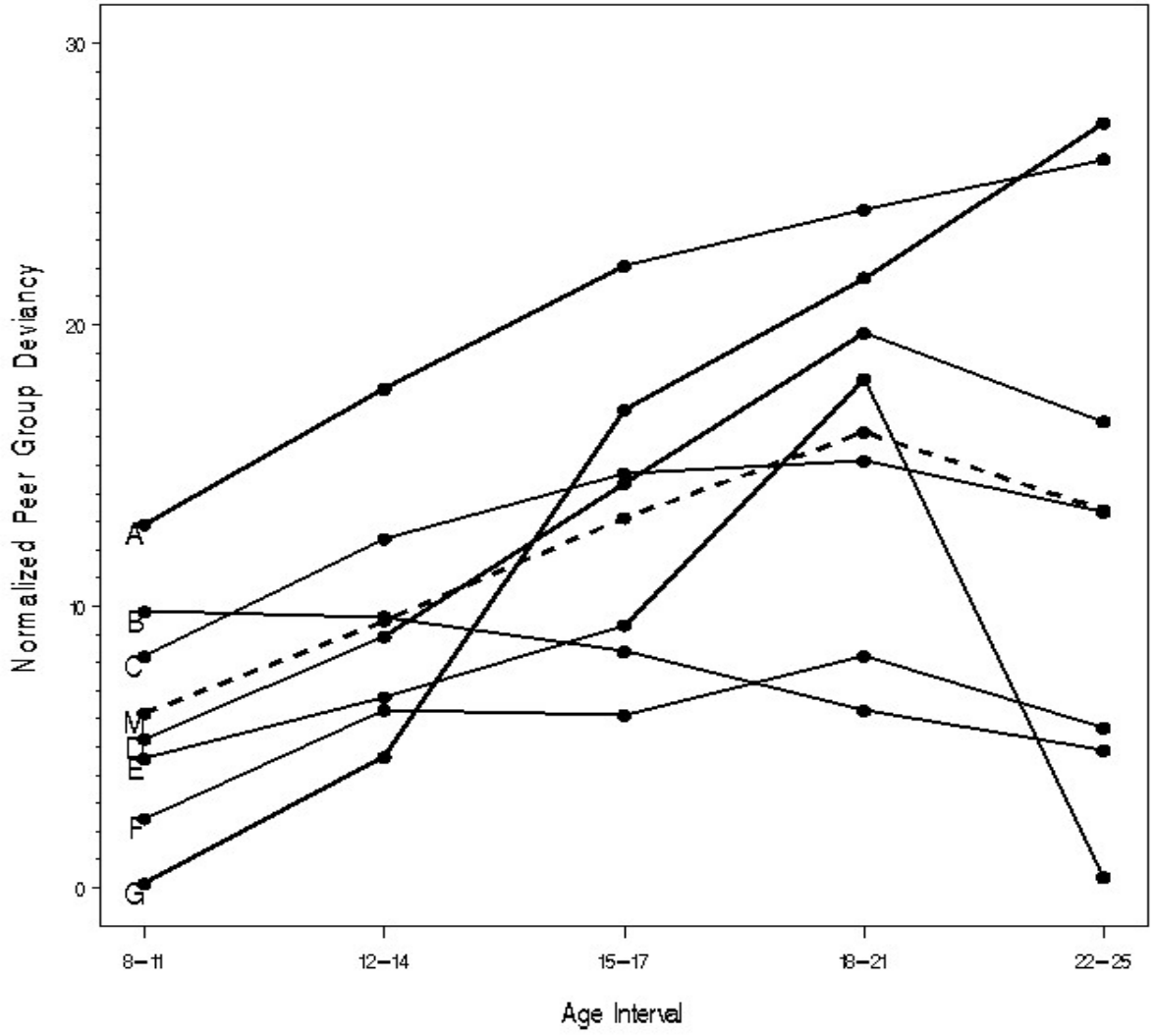
- How to begin to understand the developmental pathways through which genetic and environmental risk factors contribute to externalizing disorders.
- Do we need to move away from the static model of genetic effects that are often assumed in cross-sectional twin studies and in linkage and association studies?

Examples of Items for PGD

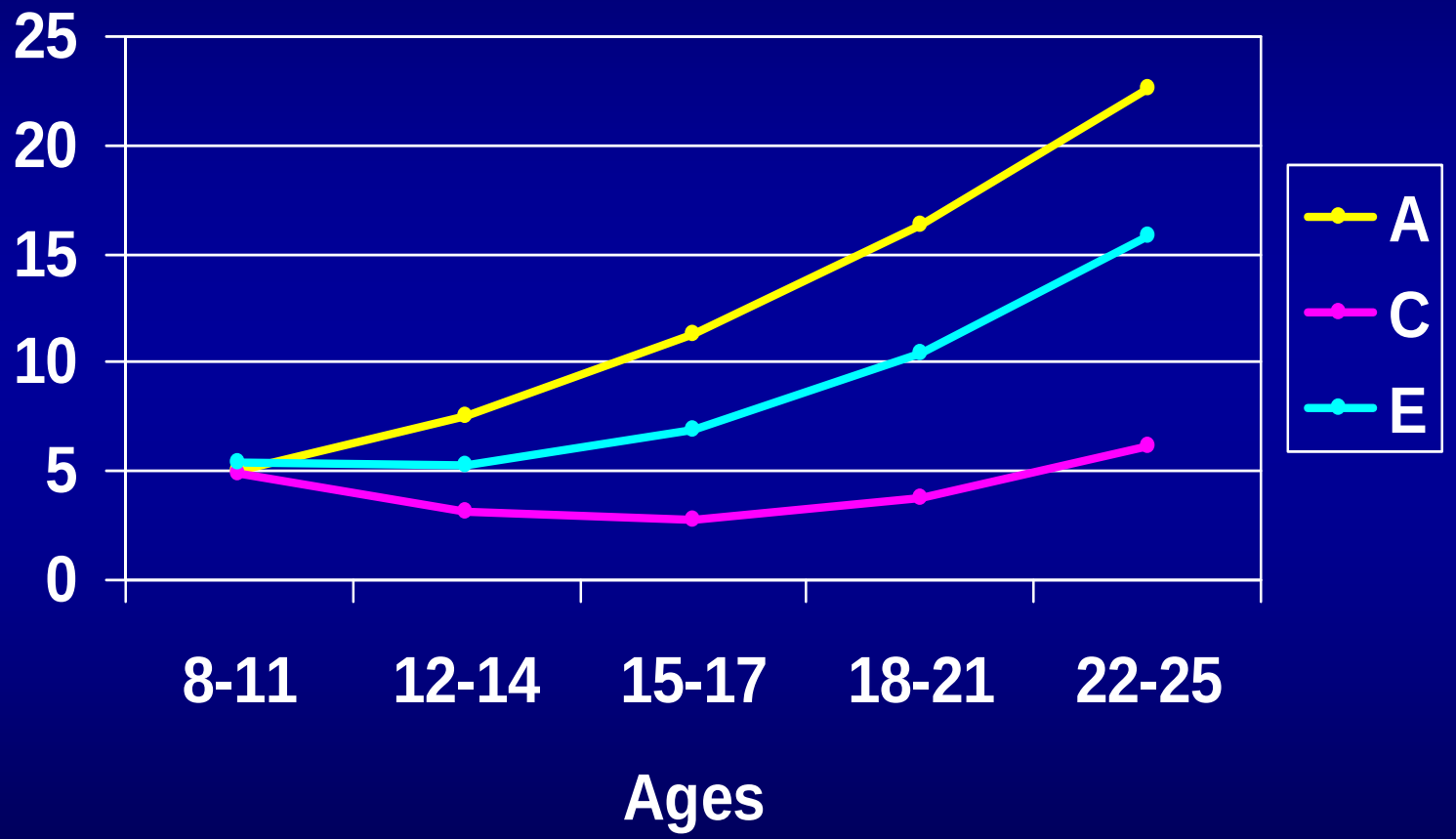
- How many of your friends would have
  - Smoked cigarettes
  - Had problems with alcohol
  - Been in trouble with the law
  - Cheated on school tests
  - Sold or gave drugs to other kids

Modeling Time and the Environment Together – Dynamic Changes in our Social Environment

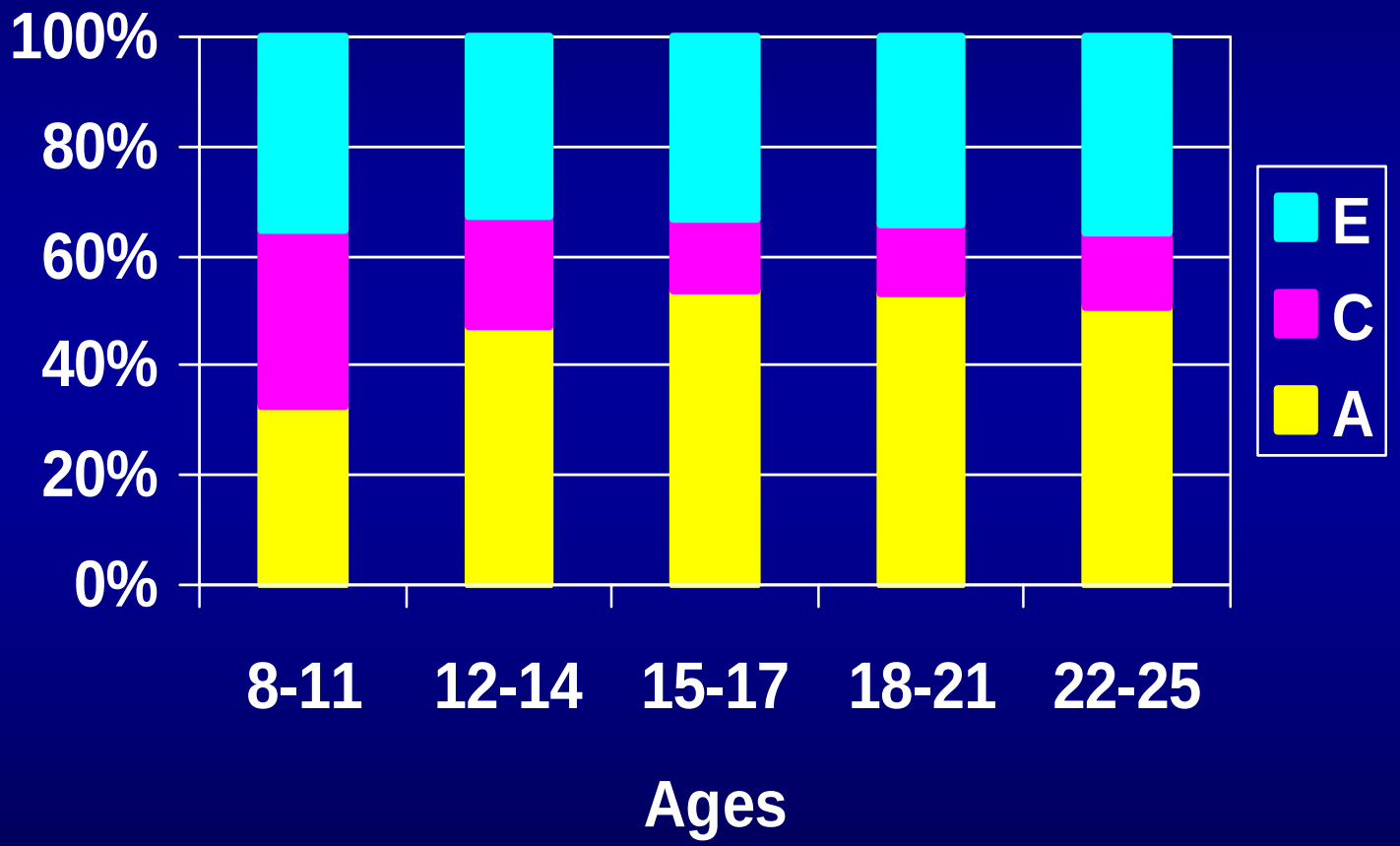
- Measures of peer group deviance retrospectively reported by the life history method.
- ~750 male-male twin pairs.
- Five ages assessed.
- The third interview wave, restricted to male-male twins, was completed in 1998-2004 by 1796 male twins (75%) who had participated in the second interview. Subjects were 24-62 years old (mean age = 40.3 years, SD = 9.0).

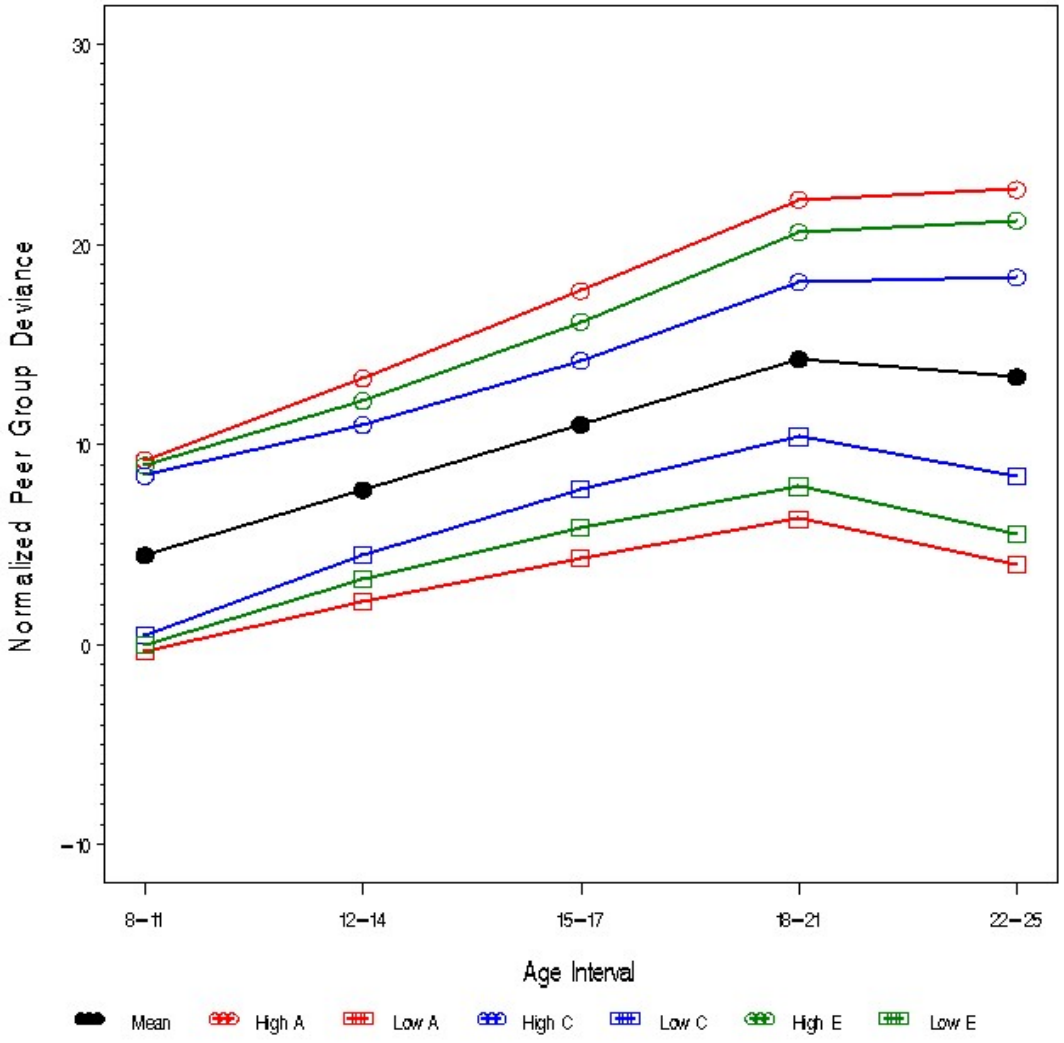

Normalized Peer Group Deviancy
30
20
10
0
A
B
C
M
F
T
G
8–11
12–14
15–17
18–21
22–25
Age Interval

Peer Group Deviance



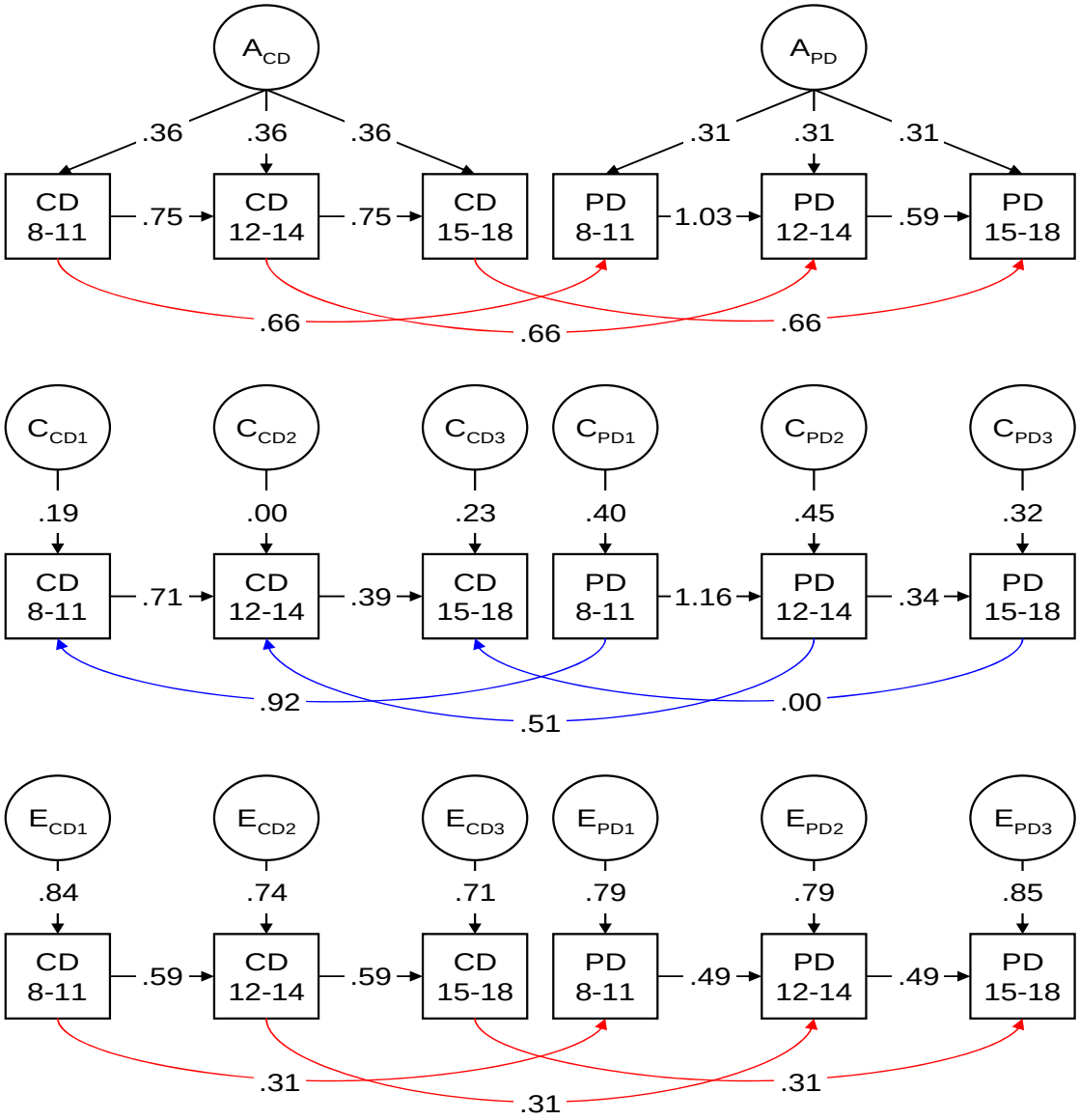
Peer Group Deviance




Normalized Peer Group Deviance
30
20
10
0
-10
8-11
12-14
15-17
18-21
22-25
Age Interval
Mean
High A
Low A
High C
Low C
High E
Low E

Joint Developmental Models for PGD and CD

- Same Sample
- Focus on 3 waves – the relationship between personal deviance (CD) and Peer group deviance (PGD)
- Major prior theories
  - Role of **social selection** CD to PD
  - Versus **social causation** PD to CD


A_CD
A_PD
.36
.36
.36
.31
.31
.31
CD 8-11
.75
CD 12-14
.75
CD 15-18
PD 8-11
1.03
PD 12-14
.59
PD 15-18
.66
.66
.66
C_CD1
C_CD2
C_CD3
C_PD1
C_PD2
C_PD3
.19
.00
.23
.40
.45
.32
CD 8-11
.71
CD 12-14
.39
CD 15-18
PD 8-11
1.16
PD 12-14
.34
PD 15-18
.92
.51
.00
E_CD1
E_CD2
E_CD3
E_PD1
E_PD2
E_PD3
.84
.74
.71
.79
.79
.85
CD 8-11
.59
CD 12-14
.59
CD 15-18
PD 8-11
.49
PD 12-14
.49
PD 15-18
.31
.31
.31

Models of Development

- Conclusions
  - Variance in peer group deviance grows dramatically with age – most of this is driven by increasing genetic effects. Genes influence how we shape our social world.

Models of Development

- Conclusions
  - Analyses of CD and PD were very illuminating about causal processes. Seems that genetic epidemiologic methods are here able to cleanly divide causal processes – social selection and social causation -- in ways that would be hard to see doing with other methods.

Summary of Talk

1. Genetic risk factors for alcohol abuse/dependence are partly specific and partly non-specific.
2. In early adolescence, shared environmental factors play an important role in individual differences in alcohol intake. With increasing age, genetic factors become more important.

Summary of Talk

3. Examine the sources of individual differences over development in self-ratings of alcohol availability.

4. Through development, genetic factors become increasingly important in influencing our choice of social environment.

5. Genes appear to drive processes of social selection (from individual to peer deviance) while shared environmental factors drive social causation (from peer to individual deviance).

Summary of Talk

6. Implications of these findings for molecular genetic studies of alcohol dependence.

Thanks

- Lindon Eaves
- John Myers
- Eric Schmitt
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- Steve Aggen
- Carol Prescott
- Nathan Gillispie
- NIH grants AA-011408 and DA-011287
- And always, the twins.