Genetic Dominance in Extended Pedigrees:

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Netherlands Twin Register

Dominance and Personality

•Nonadditive genetic variance

Individual differences due to effects of alleles (dominance) or loci (epistasis) that interact with other alleles or loci.

•Prevalent in Personality:

Keller, M. C., Coventry, W. L., Heath, A. C., & Martin, N. G. (2005). Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. *Behavior Genetics, 35,* 707-721.

Penke, L., Denissen, J. J., & Miller, G. F. (2007). The evolutionary genetics of personality. *European Journal of Personality, 21,* 549-587.

Genetic relatedness of DZ twins

Father / **Mother**

	A_1	A_2
A_3	A_3A_1	A_3A_2
A_4	A_4A_1	A_4A_2

Possible Siblings

	A_3A_1	A_3A_2	A_4A_1	A_4A_2
A_3A_1	2	1	1	0
A_3A_2	1	2	0	1
A_4A_1	1	0	2	1
A_4A_2	0	1	1	2

Average number of alleles shared:

$$\left(0 \times \frac{4}{16}\right) + \left(1 \times \frac{8}{16}\right) + \left(2 \times \frac{4}{16}\right) = 1$$

25% non-additive genetic effects

50% additive genetic effects

ADE with Classic Twin Design: Identification

If $r_{DZ} > \frac{1}{2} r_{MZ}$

$V = 1 = h^2+c^2+e^2$

$$r_{MZ} = h^2 + c^2$$

$$r_{DZ} = \frac{1}{2} h^2 + c^2$$

$$h^2 = 2(r_{MZ} - r_{DZ})$$

$$c^2 = r_{MZ} - h^2$$

$$e^2 = 1 - r_{MZ}$$

If $r_{DZ} < \frac{1}{2} r_{MZ}$

$V = 1 = a^2+d^2+e^2$

$$r_{MZ} = a^2 + d^2$$

$$r_{DZ} = \frac{1}{2} a^2 + \frac{1}{4} d^2$$

$$a^2 = 4r_{DZ} - r_{MZ}$$

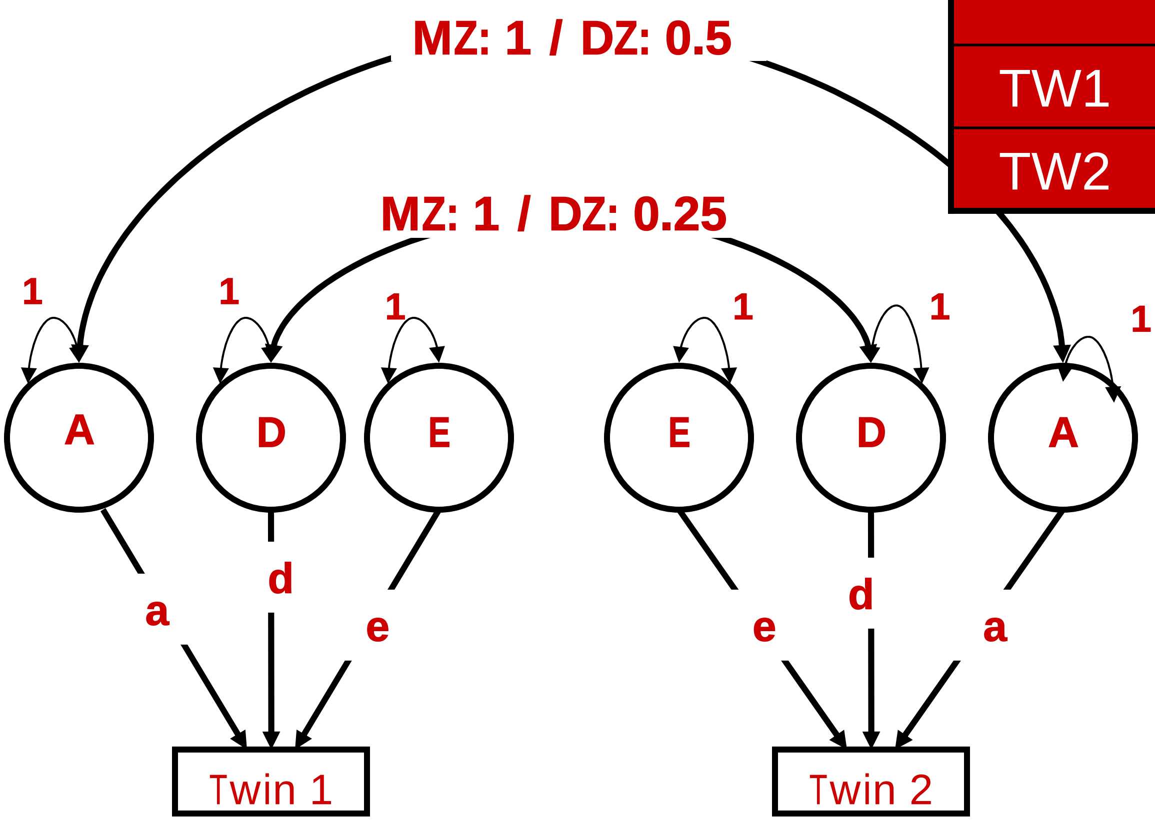
$$d^2 = 2r_{MZ} - 4r_{DZ}$$

$$e^2 = 1 - r_{MZ}$$

ADE with Classic Twin Design

MZ twin covariance matrix		
	TW1	TW2
TW1	$a^2+d^2+e^2$	a^2+d^2
TW2	a^2+d^2	$a^2+d^2+e^2$

DZ twin covariance matrix		
	TW1	TW2
TW1	$a^2+d^2+e^2$	$0.5a^2+0.25d^2$
TW2	$0.5a^2+0.25d^2$	$a^2+d^2+e^2$



If $r_{MZ} > 2r_{DZ}$ → ADE. But…Identification ≠ Power

- 95%CI of A and D include 0
- AE model fits as well as ADE: A gets inflated when D=0
- DE (although non possible) fits as well as ADE
- E model fits significantly worse then ADE model
- Large SE and large CI

- If you only have twin data, test the power of your sample size. Otherwise, restrict your conclusions to broad heritability (acknowledging possible D)
- If you have parental data…Stay with us..

Power

- Definition: The expected proportion of samples in which we decide correctly against the null hypothesis
- Depends on:
  - Effect considered (e.g. A or D)
  - Size of the effect in the population
  - Probability level adopted
  - Sample size
  - Composition of the sample: which kinds of relatives and in which proportion?
  - Level of measurement (categorical, ordinal, continuous)

(p.191;Neale & Cardon, 1992)

Power of Classic Twin Design

Mx Script → powerADEtwins.mx

```
! Step 1: Simulate the data for power
calculation of ACE model
! 30% additive genetic (.5477²=.3)
! 20% common environment (.4472²=.2)
! 50% random environment (.7071²=.5)

  #NGroups 3
G1: model parameters
  Calculation
 Begin Matrices;
          X Lower 1 1 Fixed ! genetic structure
          W Lower 1 1 Fixed ! non-additive genetic structure
          Z Lower 1 1 Fixed ! specific environmental structure
          H Full 1 1
          Q Full 1 1
 End Matrices;
```

Power of Classic Twin Design (cont.)

```
Matrix X .5477
Matrix W .4472
Matrix Z .7071
Matrix H .5
Matrix Q .25

Begin Algebra;
        A= X*X' ;
        D= W*W' ;
        E= Z*Z' ;
End Algebra;
End
```

2

```
G2: MZ twin pairs
  Calculation NInput_vars=2
 Matrices= Group 1

  Covariances A+D+E | A+D _
                 A+D   | A+D+E ;
 Options MX%E=mzsim.cov
End

G3: DZ twin pairs
  Calculation NInput_vars=2
 Matrices= Group 1
  Covariances A+D+E | H@A+Q@D _
              H@A+Q@D | A+D+E ;
Options MX%E=dzsim.cov
End
```

3

Power of Classic Twin Design (cont.)

```
!________________________________
! Step 2: Fit the wrong model to the
simulated data

#NGroups 3
G1: model parameters
  Calculation
 Begin Matrices;
            X Lower 1 1 Free
            W Lower 1 1 Fixed
            Z Lower 1 1 Free
            H Full 1 1
            Q Full 1 1
 End Matrices;

 Matrix H .5
 Matrix Q .25
```

4

```
Begin Algebra;
            A= X*X' ;
            D= W*W' ;
            E= Z*Z' ;
 End Algebra;
 End

G2: MZ twin pairs
  Data NInput_vars=2
NObservations=1000
  CMatrix Full File=mzsim.cov
 Matrices= Group 1

  Covariances A+D+E | A+D _
                 A+D   | A+D+E ;
Option RSiduals
End
```

5

Power of Classic Twin Design (cont.)

```
G3: DZ twin pairs
  Data NInput_vars=2
NObservations=1000
  CMatrix Full File=dzsim.cov

 Matrices= Group 1

  Covariances A+D+E | H@A+Q@D _
                  H@A+Q@D | A+D+E ;
Start .5 All
Options RSiduals Power= .1,1 ! for 1
tailed .05 probability value & 1 df
End
```

Power of Classic Twin Design (cont.)

Mx Output → powerADEtwins.mxo

```
! STEP 1: SIMULATE THE DATA FOR POWER CALCULATION OF
ACE MODEL
! 30% ADDITIVE GENETIC (.5477²=.3)
! 20% COMMON ENVIRONMENT (.4472²=.2)
! 50% RANDOM ENVIRONMENT (.7071²=.5)
(….)

Your model has    0 estimated parameters and      0 Observed statistics

 Chi-squared fit of model >>>>>>>     0.000
 Degrees of freedom >>>>>>>>>>>>>         0
  Probability incalculable
 Akaike's Information Criterion >     0.000
 RMSEA >>>>>>>>>>>>>>>>>>>>>>>>>>>     0.000
```

Power of Classic Twin Design (cont.)

! STEP 2: FIT THE WRONG MODEL TO THE SIMULATED DATA
(…)
Your model has 2 estimated parameters and 6 Observed statistics
Chi-squared fit of model >>>>>>> 2.573
Degrees of freedom >>>>>>>>>>>>> 4
Probability >>>>>>>>>>>>>>>>>>>> 0.632
Akaike's Information Criterion > -5.427
RMSEA >>>>>>>>>>>>>>>>>>>>>>>>>> 0.006
Power of this test, at the 0.1000 significance level with 1. df is 0.484291
Based on your combined observed sample size of 2000.

The following sample sizes would be required to reject the hypothesis:

Power	Total N
.25	710.
.50	2100.
.75	4181.
.80	4806.
.90	6657.
.95	8413.
.99	12259.

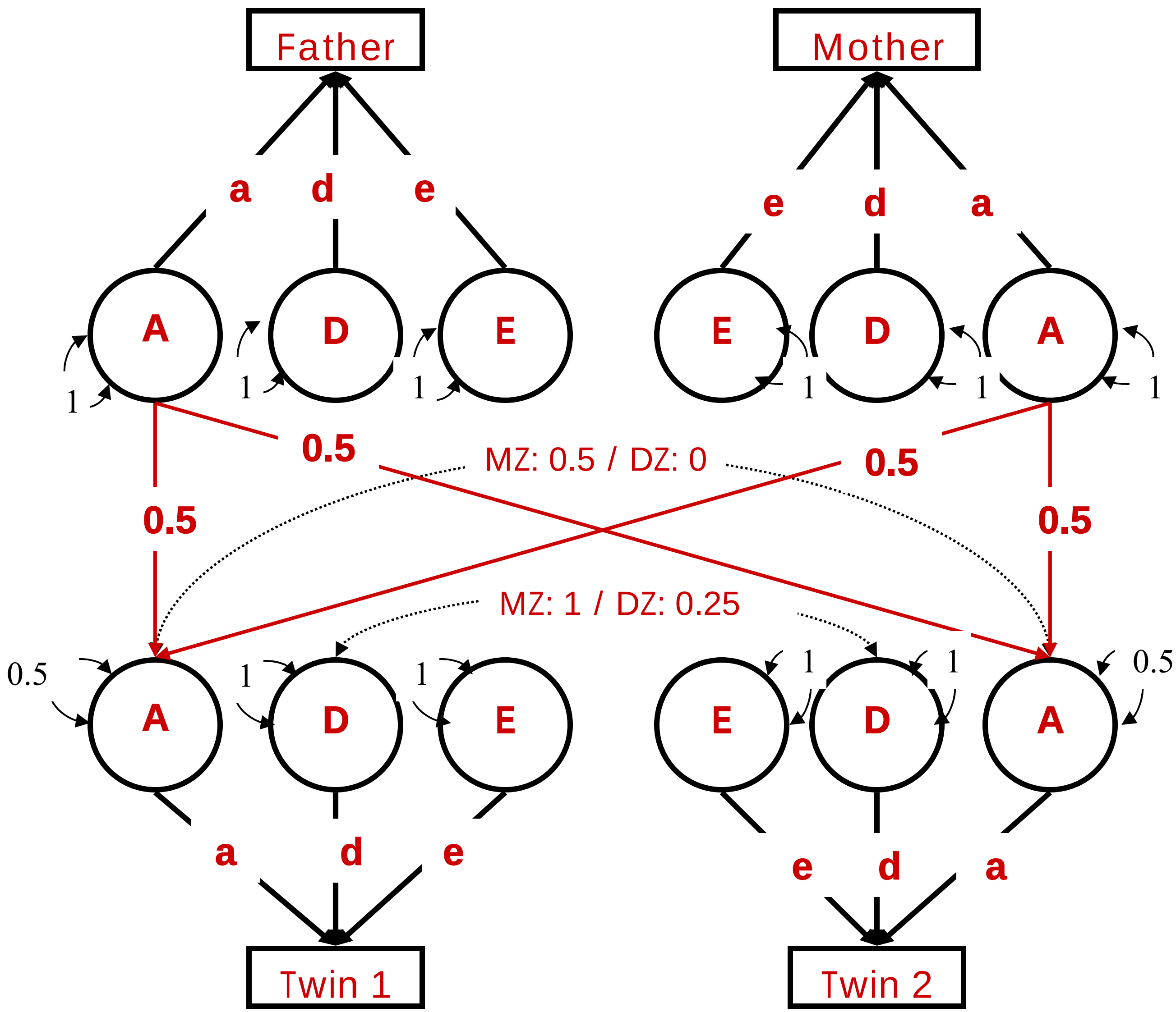
Power of Classic Twin Design (cont.)

Mx Practical → Adapt the script to investigate the power under different conditions:

- 30% A, 10% D, 60% E
- 20% A, 30% D, 50% E
- MZ/DZ ratio 2/1
- MZ/DZ ratio 1/2

MZ/DZ	Parameter tested	Power	Total N Families CTD
ADE: Va = .30, Vd = .20, Ve = .50			
1/1	Vd	**.80**	**4806 (9612)**
		.90	6657
		.95	8413
		.99	12259
2/1	Vd	**.80**	**6751 (13502)**
		.90	9351
		.95	11817
		.99	17221
1/2	Vd	**.80**	**4068 (8136)**
		.90	5634
		.95	7120
		.99	10376
ADE: Va = .30, Vd = .10, Ve = .60			
1/1	Vd	**.80**	**20836 (41672)**
		.90	28862
		.95	36474
		.99	53151
ADE: Va = .20, Vd = .30, Ve = .50			
1/1	Vd	**.80**	**2165 (4330)**
		.90	2999
		.95	3790
		.99	5523

ADE with Twins+Parents



ADE with Twins+Parents

$r_{MZ} = a^2 + d^2$

$r_{DZ} = ½\ a^2 + ¼\ d^2$

$r_{po} = ½\ a^2$

Twin-Twin

DZ twin covariance matrix				
	TW1	TW2	F	M
TW1	$a^2+d^2+e^2$			
TW2	$0.5a^2+0.25d^2$	$a^2+d^2+e^2$		
F	$0.5a^2$	$0.5a^2$	$a^2+d^2+e^2$	
M	$0.5a^2$	$0.5a^2$	0	$a^2+d^2+e^2$

Parents-offspring

Spouses

Power of EFD: Twins + Parents

Mx Script → powerADEtwins+parents.mx

```
! Step 1: Simulate the data for power calculation of ADE model
! 30% additive genetic (.5477²=.3)
! 20% Non Additive genetic (.4472²=.2)
! 50% random environment (.7071²=.5)

  #NGroups 3
G1: model parameters
  Calculation
 Begin Matrices;
          X Lower 1 1 Fixed ! genetic structure
          W Lower 1 1 Fixed ! non-additive genetic structure
          Z Lower 1 1 Fixed ! specific environmental structure
          H Full 1 1
          Q Full 1 1
          O Zero 1 1
 End Matrices;
```

Power of EFD: Twins + Parents (cont.)

```
Begin Algebra;
              A= X*X' ;
              D= W*W' ;
              E= Z*Z' ;
 End Algebra;
 End

G2: MZ twin pairs
  Calculation NInput_vars=2
 Matrices= Group 1

  Covariances A+D+E | A+D     | H@A   | H@A _
              A+D     | A+D+E | H@A   | H@A _
              H@A     | H@A     | A+D+E | O     _
              H@A     | H@A     | O         | A+D+E ;

 Options MX%E=mzsim.cov
End
```

Power of EFD: Twins + Parents (cont.)

```
Begin Algebra;
        A= X*X' ;
        D= W*W' ;
        E= Z*Z' ;
 End Algebra;
 End

G2: MZ twin pairs
  Calculation NInput_vars=2
 Matrices= Group 1
                   Twin 1     Twin 2   | Father  Mother
  Covariances A+D+E | A+D     | H@A   | H@A _
              A+D   | A+D+E   | H@A   | H@A _
              H@A   | H@A     | A+D+E | O   _
              H@A   | H@A     | O     | A+D+E ;

 Options MX%E=mzsim.cov
End
```

Twin-Twin

Parent-offspring

Spouses

Power of EFD: Twins + Parents (cont.)

```
G3: DZ twin pairs
  Calculation NInput_vars=2
 Matrices= Group 1
  Covariances A+D+E        | H@A+Q@D | H@A    | H@A _
              H@A+Q@D | A+D+E   | H@A    | H@A _
              H@A     | H@A     | A+D+E | O   _
              H@A     | H@A     | O     | A+D+E ;
Options MX%E=dzsim.cov
End
```

Power of EFD: Twins + Parents (cont.)

```
!______________________________
! Step 2: Fit the wrong model
to the simulated data

#NGroups 3
G1: model parameters
   Calculation
 Begin Matrices;
              X Lower 1 1 Free
              W Lower 1 1 Fixed
              Z Lower 1 1 Free
              H Full 1 1
              Q Full 1 1
              O Zero 1 1
 End Matrices;
 Matrix H .5
 Matrix Q .25
```

4

```
Begin Algebra;
              A= X*X' ;
              D= w*w' ;
              E= Z*Z' ;
 End Algebra;
 End

G2: MZ twin pairs
  Data NInput_vars=4 Observations=1000
  CMatrix Full File=mzsim.cov
 Matrices= Group 1

  Covariances
A+D+E | A+D    | H@A   | H@A _
A+D    | A+D+E | H@A   | H@A _
H@A    | H@A    | A+D+E | O   _
H@A    | H@A    | O     | A+D+E ;
Option RSiduals
End
```

5

Power of EFD: Twins + Parents (cont.)

```
G3: DZ twin pairs
  Data NInput_vars=4 NObservations=1000
  CMatrix Full File=dzsim.cov

 Matrices= Group 1

  Covariances A+D+E   | H@A+Q@D | H@A   | H@A _
              H@A+Q@D | A+D+E   | H@A   | H@A _
              H@A     | H@A     | A+D+E | O   _
              H@A     | H@A     | O     | A+D+E ;
Start .5 All
Options RSiduals Power= .01,1 ! for 1 tailed .05 probability value & 1 df
End
```

Power of EFD: Twins + Parents (cont.)

Mx Script → powerADEtwins+parents.mxo

Your model has 2 estimated parameters and 20 Observed statistics
Chi-squared fit of model >>>>>>>> 43.582
Degrees of freedom >>>>>>>>>>>>>> 18
Probability >>>>>>>>>>>>>>>>>>>>>> 0.001
Akaike's Information Criterion > 7.582
RMSEA >>>>>>>>>>>>>>>>>>>>>>>>>>>> 0.030
Power of this test, at the 0.0500 significance level
with 1. df is 0.999998
Based on your combined observed sample size of 2000.
The following sample sizes would be required to reject the hypothesis:

Power	Total N
.25	166.
.50	304.
.75	485.
.80	536.
.90	683.
.95	817.
.99	1103.

Power of EFD: Twins + Parents (cont.)

Mx Practical → Adapt the script to investigate the power under different conditions:

- 30% A, 10% D, 60% E
- 20% A, 30% D, 50% E
- MZ/DZ ratio 2/1
- MZ/DZ ratio 1/2

MZ/DZ	Parameter tested	Power	Total N Families CTD	TpP
ADE: Va = .30, Vd = .20, Ve = .50				
1/1	Vd	**.80**	**4806 (9612)**	**284 (1136)**
		.90	6657	393
		.95	8413	497
		.99	12259	724
2/1	Vd	**.80**	**6751 (13502)**	**244 (976)**
		.90	9351	338
		.95	11817	427
		.99	17221	622
1/2	Vd	**.80**	**4068 (8136)**	**363 (1452)**
		.90	5634	503
		.95	7120	636
		.99	10376	926
ADE: Va = .30, Vd = .10, Ve = .60				
1/1	Vd	**.80**	**20836 (41672)**	**1241 (4964)**
		.90	28862	1719
		.95	36474	2173
		.99	53151	3166
ADE: Va = .20, Vd = .30, Ve = .50				
1/1	Vd	**.80**	**2165 (4330)**	**140 (560)**
		.90	2999	194
		.95	3790	245
		.99	5523	357

Assumptions and limitations

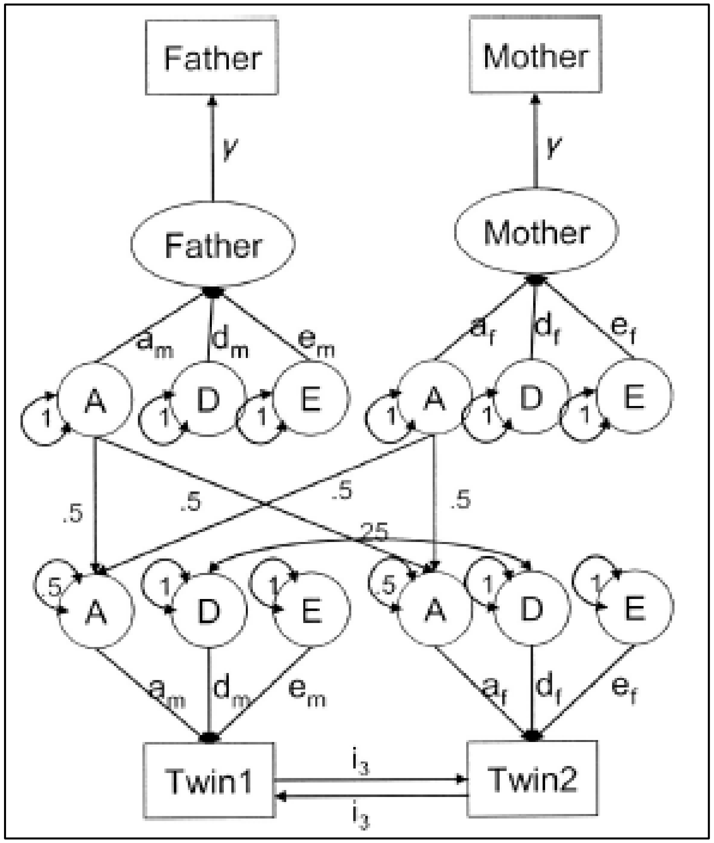
- The model assumes no generational differences in the variance components
- The use of a scalar can help to solve a difference in the total variance
- Measurement issue: Same instrument for parents and offspring?
- Implementing the model becomes more problematic with complex models: e.g. GxE
- Dominance and Contrast effects might be confounded: Beware of variance differences between MZs and DZs

Mx Practical, Real Data: Dominance in TAB

Genetic and Environmental Influences on Type A Behavior Pattern: Evidence From Twins and Their Parents in The Netherlands Twin Register

IRENE REBOLLO, MS, AND DORRET I. BOOMSMA, PHD

Psychosomatic Medicine 68:437–442 (2006)
0033-3174/06/6803-0437



The complete sample consists of 1670 families

	n (Pairs)	Correlation	99% Confidence Interval
MZM	270	0.493	0.396–0.578
MZF	372	0.472	0.389–0.547
DZM	253	0.063	−0.063–0.188
DZF	294	0.120	0.008–0.230
OS	481	0.142	0.054–0.229
Father–son (FS)	1259	0.117	0.059–0.176
Father–daughter (FD)	1483	0.178	0.124–0.232
Mother–son (MS)	1407	0.133	0.106–0.208
Mother–daughter (MD)	1678	0.157	0.078–0.187
Spouses	1359	0.015	−0.038–0.068

Mx Practical, Real Data: Matrices

Mx Script → TAB_ADE.mx

Males	Females	Others
X=[a], A=[a²]	J=[a], T=[a²]	H=[0.5]
W=[d], D=[d²]	Y=[d], U=[d²]	Q=[0.25]
Z=[e], E=[e²]	L=[e], V=[e²]	S=[γ]: Scalar
		F=[0]: Spouse correlation
		G=[m_T m_T m_F m_M]: Means

MZM

TwinM-TwinM

```
R = A+D+E     | A+D        | H@A     | H@(X*J') _
    A+D       | A+D+E      | H@A     | H@(X*J') _
    H@A       | H@A        | A+D+E | F          _
    H@(J*X')| H@(J*X') | F        | T+U+V    ;
```

Parents-offspring

Spouses

Mx Practical, Real Data: Matrices

Males	Females	Others
X=[a], A=[a^2]	J=[a], T=[a^2]	H=[0.5]
W=[d], D=[d^2]	Y=[d], U=[d^2]	Q=[0.25]
Z=[e], E=[e^2]	L=[e], V=[e^2]	S=[γ]: Scalar
		F=[0]: Spouse correlation
		G=[m_T m_T m_F m_M]: Means

DZF

TwinF-TwinF

```
R = T+U+V        | H@T+Q@U | H@(J*X')| H@T _
    H@T+Q@U | T+U+V        | H@(J*X')| H@T _
    H@(X*J')     | H@(X*J')     | A+D+E    | F   _
    H@T          | H@T          | F        | T+U+V   ;
```

Parents-offspring

Spouses

Mx Practical, Real Data: Matrices

Males	Females	Others
X=[a], A=[a^2]	J=[a], T=[a^2]	H=[0.5]
W=[d], D=[d^2]	Y=[d], U=[d^2]	Q=[0.25]
Z=[e], E=[e^2]	L=[e], V=[e^2]	S=[γ]: Scalar
		F=[0]: Spouse correlation
		G=[m_T m_T m_F m_M]: Means

OSMF

TwinM-TwinF

```
R = A+D+E                | H@(X*J')+Q@(W*Y') | H@A          | H@(X*J') _
    H@(J*X')+Q@(Y*W')    | T+U+V             | H@(J*X')     | H@T      _
    H@A                  | H@(X*J')          | A+D+E        | F  _
    H@(J*X')             | H@T               | F            | T+U+V   ;
```

Parents-offspring

Spouses

Mx Practical, Real Data: Matrices

Scalar Matrix B= N | (N@S)_
(N@S) | (N@(S*S'));

<u>Matrix B (dot) multiplies Matrix R:</u>

The Twin-Twin covariance is unaffected

Then Parent-Twin covariance is multiplied by γ

The Parent-Parent covariance is multiplied by γ^2

$$S = \gamma$$

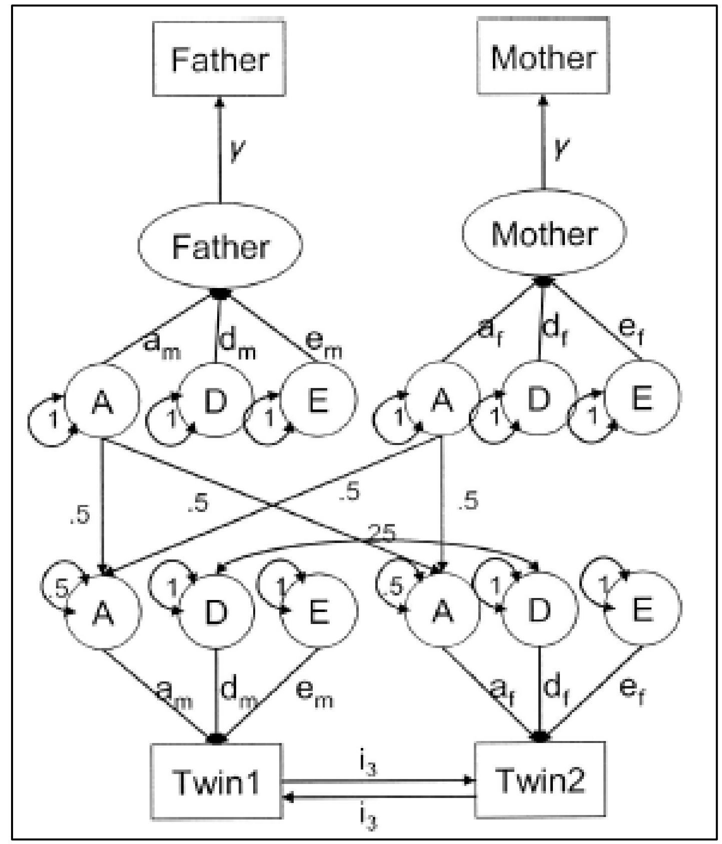
$$N = \begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}$$

$$B = \left[\begin{array}{cc|cc} 1 & 1 & \gamma & \gamma \\ 1 & 1 & \gamma & \gamma \\ \hline \gamma & \gamma & \gamma^2 & \gamma^2 \\ \gamma & \gamma & \gamma^2 & \gamma^2 \end{array}\right]$$

Twin-Twin

Parent-Twin

Parent-Parent



Mx Practical, Real Data: Practice

Open the Script: TAB_ADE.mx

Use the Multiple Option to test:

- Equality of variance components for males and females
- D=0
- S=1

Write down the estimates of the proportions of variance explained by A, D and E in your final model.

Mx Practical, Real Data: Results

Twins + Parents

Model	-2LL	*df*	$\chi^2(df)$	p
Full	35698.95	6202		
ADE_m=ADE_f	**35706.36**	**6205**	**7.411(3)**	**.060**
D=0	35726.21	6206	19.844(1)	<.001
S=1	35783.36	6206	77.000(1)	<.001

Only Twins

Model	-2LL	*df*	$\chi^2(df)$	p
Full	18282.94	3265		
ADE_m=ADE_f	**18283.54**	**3268**	**.605(3)**	**.895**
D=0	18295.95	3269	12.40(1)	<.001

		Twins+ parents	Twins
A	Estimate	**.28**	**.04**
	CI	.23-.34	.00-.25
D	Estimate	**.17**	**.43**
	CI	.10-.25	.21-.53
E	Estimate	.54	.53
	CI	.48-.59	.47-.58