Comorbidity Models

Michael C Neale
Virginia Institute for Psychiatric and Behavioral Genetics VCU

International Workshop on Methodology for Genetic Studies
Boulder Colorado 5\textsuperscript{th} March 2010

Friday, March 5, 2010
Overview

• Psychiatric Disorders: binary phenotypes
  – Lots of comorbidity
  – Substance abuse similar
• ACE model is but one of many
• Two twins, two binary variables
  – 16 outcome combinations
• Fit models by maximum likelihood
  – (alternatives exist)
Assessment of Psychiatric Disorders

- Psychiatrists can agree on symptoms better than on diagnoses (Kendell et al 1971)


- Little empirical basis for classification

- “If you believe…”
Comorbidity is High

• High for Psychiatric Disorders
  – Anxiety
  – Depression
  – Phobias
  – Panic
  – Alcohol Abuse

• 70% of those with history of 1 have history of at least one other (Kessler 1993; N=18,000)

• Similar rates in 10,000+ Virginia twins
Pure forms of two disorders A & B generate some of the same symptoms.
Assessments of disorders A & B share some symptoms

Cramer, Waldrop, Van der Maas, Borsboom (In Press)
Comorbidity: A network perspective.  Brain Behavior Sciences

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Comorbidity due to symptom sharing

A few characteristics of the MDD and GAD comorbidity network stand out in particular (see Figure 4). First, GAD symptoms are more frequent than MDD symptoms (i.e., GAD nodes are generally larger than MDD nodes). At first sight, this may appear at odds with the higher prevalence of MDD compared to GAD that is usually reported (Carter, Wittchen, Pfister & Kessler, 2001; Kessler, Chiu, Demler & Walters, 2005). However, on a diagnosis level, only

4. The basic structure of the depression and generalized anxiety comorbidity network

We have checked the stability of the results depicted in this figure by randomly splitting the sample in two and run all analyses for both groups separately. Those separate analyses revealed the same results and thus, we consider the components of Figure 4 to be stable.

Not today!

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Why do people get a disorder?

Single factor of large effect?
Lots of little factors of cumulative effect?
Both?

How do we find out which?
  Measure variation
  Measure covariation to understand it

Basic statistical theory
Two Dimensions: Contours

- High correlation
- Low correlation

Disorder 1

Disorder 2
Non-normal distribution: Contours

Twin 1

Twin 2
Basic Theory

• Models for symptoms:
  – Latent class analysis
  – Factor analysis
  – Factor mixture model
  – Reprieved...

Models of Comorbidity for Multifactorial Disorders
Michael C. Neale¹ and Kenneth S. Kendler¹²
Departments of ¹Psychiatry and ²Human Genetics, Medical College of Virginia, Richmond
Comorbidity

A correlation between (binary) traits
Neale & Kendler (1995)  13 Models
Based on Klein & Riso (1994)

\[ r \]

MDD -> GAD
Partitioning Comorbidity

\[ r_A \]

\[ r_C \]

\[ r_E \]

\[ A_D \] \[ C_D \] \[ E_D \] \[ MDD \]
\[ a_D \] \[ c_D \] \[ e_D \]

\[ E_A \] \[ C_A \] \[ A_A \] \[ GAD \]
\[ a_A \] \[ c_A \] \[ e_A \]
Modeling Comorbidity

Reciprocal Causation
Modeling Comorbidity
Major Depression Causes Generalized Anxiety Disorder
Modeling Comorbidity

Generalized Anxiety Disorder causes Major Depression
Alternative models of increasing risk to a second disorder

\[ p(\text{comorbid}) = \text{chance of getting second disorder} \]

- Threshold Model \( r = 0.5 \)
- Causal/Correlational Model
- Jump Model

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Alternate forms: One underlying continuum
Alternate forms: More detail

\[ L = \int_{-\infty}^{t_1} \phi(R) dR \quad (1) \]

\[ M = \int_{t_1}^{t_2} \phi(R) dR \quad (2) \]

\[ U = \int_{t_2}^{\infty} \phi(R) dR . \quad (3) \]

\[ P(\overline{A}, \overline{B}) = L + (1 - p)(1 - r)U \quad (4) \]

\[ P(\overline{A}, B) = p(1 - r)U \quad (5) \]

\[ P(A, \overline{B}) = (1 - p)r U \quad (6) \]

\[ P(A, B) = pr U , \quad (7) \]
Alternate forms: Detail of pairs

\[
P(\overline{A_1}, B_1, \overline{A_2}, B_2) = LL + 2(1 - p)(1 - r)UL + (1 - p)^2(1 - r)^2UU \tag{30}
\]

\[
P(\overline{A_1}, B_1, \overline{A_2}, B_2) = r(1 - p)LU + (1 - p)^2r(1 - r)^2UU \tag{31}
\]

\[
P(\overline{A_1}, B_1, A_2, B_2) = p(1 - r)LU + p(1 - p)(1 - r)^2UU \tag{32}
\]

\[
P(\overline{A_1}, B_1, A_2, B_2) = prLU + p(1 - p)r(1 - r)UU \tag{33}
\]

\[
P(\overline{A_1}, B_1, \overline{A_2}, B_2) = (1 - p)^2r^2UU \tag{34}
\]

\[
P(\overline{A_1}, B_1, A_2, B_2) = p(1 - p)r(1 - r)UU \tag{35}
\]

\[
P(\overline{A_1}, B_1, A_2, B_2) = p(1 - p)r^2UU \tag{36}
\]

\[
P(\overline{A_1}, B_1, A_2, B_2) = p^2r(1 - r)UU \tag{38}
\]

\[
P(\overline{A_1}, B_1, A_2, B_2) = p^2r^2UU \tag{39}
\]

\[
LL_A = \int_{-\infty}^{\alpha_A} \int_{-\infty}^{\alpha_A} \phi(R_{A_1}, R_{A_2})dR_{A_2}dR_{A_1} \tag{24}
\]

\[
LM_A = \int_{-\infty}^{\alpha_A} \int_{\alpha_A}^{\infty} \phi(R_{A_1}, R_{A_2})dR_{A_2}dR_{A_1} \tag{25}
\]

\[
LU_A = \int_{-\infty}^{\alpha_A} \int_{-\infty}^{\alpha_A} \phi(R_{A_1}, R_{A_2})dR_{A_2}dR_{A_1} \tag{26}
\]

\[
MM_A = \int_{\alpha_A}^{\infty} \int_{\alpha_A}^{\infty} \phi(R_{A_1}, R_{A_2})dR_{A_2}dR_{A_1} \tag{27}
\]

\[
MU_A = \int_{-\infty}^{\alpha_A} \int_{\alpha_A}^{\infty} \phi(R_{A_1}, R_{A_2})dR_{A_2}dR_{A_1} \tag{28}
\]

\[
UU_A = \int_{\alpha_A}^{\infty} \int_{\alpha_A}^{\infty} \phi(R_{A_1}, R_{A_2})dR_{A_2}dR_{A_1} \tag{29}
\]
# Program: Alternate Forms

require(OpenMx)

nv<-1

# Fit Alternate Forms Model with Cell Frequencies Input, ACE-one overall Threshold

AltFormsModel <- mxModel("AlternateForms",
  mxModel("ACE",
    # Matrices a, c, and e to store a, c, and e path coefficients
    mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE, values=.6, label="a11", name="a" ),
    mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE, values=.6, label="c11", name="c" ),
    mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE, values=sqrt(.28), label="e11", name="e" ),
    # Matrices A, C, and E compute variance components
    mxAlgebra( expression=a %*% t(a), name="A" ),
    mxAlgebra( expression=c %*% t(c), name="C" ),
    mxAlgebra( expression=e %*% t(e), name="E" ),
    # Algebra to compute total variances and standard deviations (diagonal only)
    mxAlgebra( expression=A+C+E, name="V" ),
    mxMatrix( type="Iden", nrow=nv, ncol=nv, name="I"),
    mxAlgebra( expression=solve(sqrt(I*V)), name="sd"),
    # Constraint on variance of A+C+E latent variables
    mxConstraint( alg1="V", ",=", alg2="I", name="Var1"),
  ),
)
OpenMx Script algebra for Alternate Forms

# Algebra for expected variance/covariance matrix in MZ
mxAlgebra(expression= rbind ( cbind(A+C+E , A+C),
                                cbind(A+C   , A+C+E)), name="expCovMZ" ),

# Algebra for expected variance/covariance matrix in DZ, note use of 0.5,
mxAlgebra(expression= rbind ( cbind(A+C+E , 0.5%x%A+C),
                                cbind(0.5%x%A+C , A+C+E)), name="expCovDZ" ),

# Matrices for probabilities P Q R S of being affected given below/above threshold
mxMatrix(type="Full", nrow=1, ncol=1, free=TRUE, values=.8, label="p", name="P" ),
mxMatrix(type="Full", nrow=1, ncol=1, free=TRUE, values=.6, label="r", name="R" ),
mxMatrix(type="Iden", nrow=1, ncol=1, free=F, name="I" ),
mxAlgebra(expression= I-P, name="Q" ),
mxAlgebra(expression= I-R, name="S" ),

# Threshold parameter & matrices for (fixed at zero) means
mxMatrix(type="Full", nrow=1, ncol=1, free=TRUE, values=1, label="tmz", name="T" ),
mxMatrix(type="Zero", nrow=1, ncol=nv, name="M" ),
mxAlgebra(expression= cbind(M,M), name="expMean" ),

# Integrals for computing the pairwise probabilities of being above/below threshold - MZ
mxAlgebra(expression=omxMnor(expCovMZ, expMean, cbind(-Inf,-Inf), cbind(T,T)),
  name="bothBelow"),
mxAlgebra(expression=omxMnor(expCovMZ, expMean, cbind(-Inf,T), cbind(T,Inf)),
  name="oneBelow"),
mxAlgebra(expression=omxMnor(expCovMZ, expMean, cbind(T,T), cbind(Inf,Inf)),
  name="bothAbove"),
OpenMx Script algebra for Alternate Forms

# Integrals for computing the pairwise probabilities of being above/below threshold - DZ
mxAlgebra(expression=omxMnor(expCovDZ, expMean, cbind(-Inf,-Inf), cbind(T,T)),
        name="bothBelowDZ"),
    mxAlgebra(expression=omxMnor(expCovDZ, expMean, cbind(-Inf,T), cbind(T,Inf)),
        name="oneBelowDZ"),
    mxAlgebra(expression=omxMnor(expCovDZ, expMean, cbind(T,T), cbind(Inf,Inf)),
        name="bothAboveDZ"),

# Finally, predicted proportions in each of 10 cells for MZ
mxAlgebra(rbind(
    bothBelow + 2*oneBelow*Q*S + bothAbove*Q*Q*S*S,
    2*(oneBelow*R*Q + bothAbove*Q*Q*R*S),
    2*(oneBelow*P*S + bothAbove*P*Q*S*S),
    2*(oneBelow*P*R + bothAbove*P*R*Q*S),
    bothAbove*Q*Q*R*R,
    2*bothAbove*P*Q*R*S,
    2*bothAbove*P*Q*R*R,
    bothAbove*P*S*P*S,
    2*bothAbove*P*S*P*R,
    bothAbove*P*R*P*R
),name="MZExpectedFrequencies"),
OpenMx Script algebra for Alternate Forms

# Finally, predicted proportions in each of 10 cells for DZ
mxAlgebra(rbind(
    bothBelowDZ + 2*oneBelowDZ*Q*S + bothAboveDZ*Q*Q*S*S,
    2*(oneBelowDZ*R*Q + bothAboveDZ*Q*Q*R*S),
    2*(oneBelowDZ*P*S + bothAboveDZ*P*Q*S*S),
    2*(oneBelowDZ*P*R + bothAboveDZ*P*R*Q*S),
    bothAboveDZ*Q*Q*R*R,
    2*bothAboveDZ*P*Q*R*S,
    2*bothAboveDZ*P*Q*R*R,
    bothAboveDZ*P*S*S*S,
    2*bothAboveDZ*P*S*S*P*R,
    bothAboveDZ*P*P*R*P*R, name="DZExpectedFrequencies")),

mxModel("MZ",
mxMatrix(type="Full", nrow=10, ncol=1, free=FALSE,
    values=c(141,35,32,25,15,7,33,18,39,47), name="MZObservedFrequencies"),
mxAlgebra(-2 * sum(MZObservedFrequencies * log
    (ACE.MZExpectedFrequencies)), name="MZalgobj"),
mxAlgebraObjective("MZalgobj"),

Friday, March 5, 2010
OpenMx Script algebra for Alternate Forms

```r
mxModel("DZ",
    mxMatrix(type="Full", nrow=10, ncol=1, free=F, values=c(58,18,27,44,7,6,33,15,38,81), name="DZObservedFrequencies"),
    mxAlgebra(
        -2 * sum(DZObservedFrequencies * log (ACE.DZEpectedFrequencies)),name="DZalgobj"),
    mxAlgebraObjective("DZalgobj"),
    mxAlgebra( MZ.objective + DZ.objective, name="-2sumll" ),
    mxAlgebraObjective("-2sumll"))

AltFormsRun<-mxRun(AltFormsModel)
summary(AltFormsRun)
```
Causal or correlated models
Correlated Liabilities

Inherent in OpenMx Ordinal Data Analysis
We can do it by hand as well
Jump Model: Actually having one disorder raises chance of getting second
Random Multiformity: Detail

\[ P(\overline{A}, \overline{B}) = L_A \cdot L_B \]  
(8)

\[ P(\overline{A}, B) = (1 - r)L_A \cdot U_B \]  
(9)

\[ P(A, \overline{B}) = U_A \cdot (1 - p)L_B \]  
(10)

\[ P(A, B) = U_A \cdot (U_B + pL_B) + rL_A \cdot U_B, \]  
(11)

\[ P(\overline{A}_1, B_1, \overline{A}_2, B_2) = LL_A \cdot LL_B \]  
(40)

\[ P(\overline{A}_1, B_1, \overline{A}_2, B_2) = LL_A \cdot (1 - r)LU_B \]  
(41)

\[ P(\overline{A}_1, B_1, A_2, B_2) = (1 - p)LU_A \cdot LL_B \]  
(42)

\[ P(\overline{A}_1, B_1, A_2, B_2) = LU_A \cdot (pLL_B + LU_B) \]  
(43)

\[ P(\overline{A}_1, B_1, A_2, B_2) = LL_A \cdot (1 - r)^2UU_B \]  
(44)

\[ P(\overline{A}_1, B_1, A_2, B_2) = (1 - p)LU_A \cdot (1 - r)LU_B \]  
(45)

\[ P(\overline{A}_1, B_1, A_2, B_2) = (1 - r)LU_A \cdot (pLU_B + LU_B) \]  
(46)

\[ P(\overline{A}_1, B_1, A_2, B_2) = p^2UU_A \cdot LL_B \]  
(47)

\[ P(A_1, B_1, A_2, B_2) = UU_A \cdot [(1 - p)LU_B + (1 - p)LU_B] \]  
(48)

\[ P(A_1, B_1, A_2, B_2) = 2pUU_A \cdot LU_B \]  
(49)
Three separate disorders
Three Independent Disorders

\[ P(\overline{A_1}, B_1, A_2, B_2) = L_L A \cdot L_L A_B \cdot L_L B \]  
\[ P(A_1, B_1, A_2, B_2) = L_L A \cdot L_L A_B \cdot L_U B \]  
\[ P(A_1, \overline{B_1}, A_2, B_2) = L_U A \cdot L_L A_B \cdot L_L B \]  
\[ P(A_1, \overline{B_1}, A_2, B_2) = L_L A \cdot L_L A_B \cdot L_L B \; + \; L_U A \cdot L_L A_B \cdot L_U B \]  
\[ P(A_1, B_1, A_2, B_2) = L_L A \cdot L_L A_B \cdot U_U B \]  
\[ P(A_1, B_1, A_2, B_2) = L_U A \cdot L_L A_B \cdot L_U B \]  
\[ P(A_1, B_1, A_2, B_2) = L_L A \cdot L_U A_B \cdot U_U B \; + \; L_U A \cdot L_L A_B \cdot U_U B \]  
\[ P(A_1, B_1, A_2, B_2) = U_U A \cdot L_L A_B \cdot L_L B \]  
\[ P(A_1, B_1, A_2, B_2) = L_L A \cdot L_U A_B \cdot L_U B \; + \; U_U A \cdot L_L A_B \cdot L_U B \]  
\[ P(A_1, B_1, A_2, B_2) = U_U A_B \; + \; U_U A \cdot L_L A_B \cdot U_U B \; + \; 2U_L A \cdot L_U A_B \cdot U_B \]
Unified Comorbidity Model?
Unified Genetic Comorbidity Model?
Sources for comorbidity scripts

- [http://ibgwww.colorado.edu/cadd/software](http://ibgwww.colorado.edu/cadd/software)
- Soo Rhee’s website! Excellent!
- Includes covariates e.g., age (Rhee et al submitted)
- Clinical selected samples as well
- Exercise: download and fit the examples and decide on best fit model

- [http://www.vcu.edu/mx/examples](http://www.vcu.edu/mx/examples)
- Mike Neale’s script website.
- More than a little bit dusty
OpenMx User-defined Functions

• Can specify AlgebraObjective

\[
\text{mxAlgebra( } \text{MZ.objective + DZ.objective, name="-2sumll" ),}
\text{mxAlgebraObjective("-2sumll"))}
\]

• Any mxAlgebra you like!
  – Woohoo!

• See, e.g., http://openmx.psyc.virginia.edu/repoview/1/trunk/models/passing/oneLocusLikelihood.R

• One & two locus ABO blood group examples

Friday, March 5, 2010
Comorbidity with covariates

- Soo Rhee’s website again
- http://ibgwww.colorado.edu/cadd/software
- These scripts are in classic Mx
- Look out for updates
Possible Extensions

- More than two disorders
- More than one point in time
- More than pairs of twins
- Covariates & GxE

- Models for symptoms (IRT)
- Dynamical systems models
- Generalization to continuous liability
Possible Exercises

• Modify directionofCausation.R to fit:
  – Anxiety (P2) causes depression (P1)
  – Bidirectional causation (tricky, may need bounds)
  – Test hypothesis that comorbidity in ACE bivariate is purely due to rG

• Use tableFitStatistics function to compare results of ACE & other comorbidity models

• Find some other data, rinse & repeat...
Comorbidity Depression & Anxiety Disorders

Alternate forms
Random Multiformity
Random Multiformity of MD
Random Multiformity of GAD
Extreme Multiformity
Extreme Multiformity of MD
Extreme Multiformity of GAD
Three Separate Disorders
Correlated Liability ACE
MD causes GAD
GAD causes MD
Reciprocal Causation

Better
Worse

AIC

DSM IIIR MD & Alcohol Abuse

Friday, March 5, 2010