Genetic Factors and the Directionality of Comorbid Disorders

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Getting to the root(s)

“The active ingredient in Roundup moves through the weed to kill the root.”
Phenotyping SUD

Arbitrary phenotypes—ICD-m, DSM-n

Dx of substance dependence:
≥3 out of nine symptoms
→ 466 combinations

Staging—opportunistic

Mixed effects: stimulants & depressants

\[ \sum_{k_i} \frac{n!}{k_i!(n-k_i)!} \]

And a little bit of this'd get you up
And a little bit of that'd get you down
Mark Knopfler “Junkie Doll”
“...to express not only the individual innate tendency to develop or contract the disease, i.e., his susceptibility in the usual sense, but also the whole combination of external circumstances that make him more or less likely to develop the disease...”

Falconer (1965)
Liability distribution

Affected

Liability

threshold

phenotype
Shared liability variance


**FIGURE 1.** Relationship of “common vulnerability” to vulnerability for each illicit drug category.

**FIGURE 2.** Relationship of genetic aspects of “common vulnerability” to genetic aspects of vulnerability for each illicit drug category. Proportion of variance in drug abuse attributable to genetic factors: marijuana, 33%; stimulants, 33%; sedatives, 27%; heroin/opiates, 54%; PCP/psychedelics, 26%.
More sharing


Cannabis  Cocaine  Halluc  Sedat  Stimul  Opiate

0.01/0.09  0.00/0.14  0.05/0.25  0.07/0.34  0.06/0.16  0.00/0.64
Psychiatric and drug abuse disorders

Common sources of variation

**Pre-use**
- Temperament
- Personality
- Cognition
- Behavior
- Self-medication

**Post-use**
- Positive reinforcement
- Negative reinforcement

Biobehavioral self-regulation
The drug-activated mesocorticolimbic dopamine pathway

ALCOHOL

OPIATES

COCAINENE &
AMPHETAMINES

Substantia nigra

Periaqueductal gray area

Colliculus

Ventral tegmental area

Cerebellum

Dopamine pathway

Amygdala

Hippocampus

Nucleus accumbens

Striatum

Prefrontal cortex

The drug-activated mesocorticolimbic dopamine pathway
Comorbidity models

- Chance, bias, stratification
- Alternate forms (single liability)
- Multiformity (having one increases probability of another, threshold-dependent)
- Three independent
- Correlated liabilities (threshold-independent)
  - correlated
  - one causes another
  - reciprocal causation
Subsample of models

Genetics in SUD risk

Genes in determination in variation

SUD liability
It’s a long way ...
Dynamic liability: Tracking etiology and comorbidity of SUD

Risk

Drug use

SUD

Epigenetic trajectory

Time 0

Initial liability

Time 1

Time 2

Liability

threshold

SUD
Genetics & comorbidity

- Behavior genetics
  - genetic and environmental correlations
  - developmental tracking

- Molecular genetics
  - association/linkage
  - mediation by intermediate traits

- “Hybrids”
Family history

- Faster physiological maturation
- Detachment from parents
- Homophilic peer selection/contagion
- Dysregulation/disinhibition
- Maladjustment
- SU/SUD
Transmissible causal variables (e.g., genetic polymorphisms, neurochemical processes, transmissible environment)

\[ \psi_1 \rightarrow \psi_2 \rightarrow \psi_3 \rightarrow \psi_4 \]

Psychological variables

\[ L_F \rightarrow \psi_1 \rightarrow \psi_2 \rightarrow \psi_3 \rightarrow \psi_4 \]

\[ L_P \rightarrow \psi_4 \]

L_P – parental liability
L_F – son’s liability

nontransmissible environment
## DBD and the rate of SUD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>2.81</td>
<td>1.42-5.55</td>
<td>0.003</td>
</tr>
<tr>
<td>CD</td>
<td>7.17</td>
<td>2.78-18.52</td>
<td>0.00005</td>
</tr>
<tr>
<td>ODD</td>
<td>2.20</td>
<td>1.04-4.63</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*dysregulation*
Measurement of SUD liability

\[ L_P \]

\[ L_F \]

transmissible causal variables (e.g., genetic polymorphisms, neurochemical processes, transmissible environment)

Psychological constructs

\[ \eta_4 \]
\[ \eta_3 \]
\[ \eta_2 \]
\[ \eta_1 \]

nontransmissible environment

SUDLI indicator variables (items)

\[ y_{12} \]
\[ y_{11} \]
\[ y_{10} \]
\[ y_9 \]
\[ y_8 \]
\[ y_7 \]
\[ y_6 \]
\[ y_5 \]
\[ y_4 \]
\[ y_3 \]
\[ y_2 \]
\[ y_1 \]

LP – parental liability
LF – son’s liability
DRD4-ERP-Disinhibition

- Family-based analysis (FBAT)
- Promoter region (-521) SNP
- ERP—ND: p=.02
- SNP—>P300: p=.004
- SNP—>ND: p=.003
- SNP—>ND|P300: p=.85
## Parenting & MAOA

<table>
<thead>
<tr>
<th>Dependent Sample</th>
<th>Predictor</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD full</td>
<td>dad</td>
<td>0.504 (0.289-0.879)</td>
<td>.016</td>
</tr>
<tr>
<td></td>
<td>momxdad</td>
<td>0.652 (0.456-0.932)</td>
<td>.019</td>
</tr>
<tr>
<td>4R</td>
<td>dad</td>
<td>0.380 (0.179-0.805)</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td>mom</td>
<td>1.601 (0.989-2.591)</td>
<td>.055</td>
</tr>
<tr>
<td>3R</td>
<td>dad</td>
<td>0.796 (0.343-1.850)</td>
<td>.597</td>
</tr>
<tr>
<td></td>
<td>mom</td>
<td>1.099 (0.534-2.265)</td>
<td>.797</td>
</tr>
<tr>
<td>ADHD full</td>
<td>momxdad</td>
<td>1.558 (1.031-2.353)</td>
<td>.035</td>
</tr>
<tr>
<td></td>
<td>dadxMAO</td>
<td>3.299 (1.479-7.356)</td>
<td>.004</td>
</tr>
<tr>
<td>4R</td>
<td>dad</td>
<td>1.974 (1.230-3.168)</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td>momxdad</td>
<td>1.799 (1.057-3.062)</td>
<td>.030</td>
</tr>
<tr>
<td>3R</td>
<td>dad</td>
<td>0.574 (0.256-1.284)</td>
<td>.177</td>
</tr>
<tr>
<td></td>
<td>momxdad</td>
<td>1.604 (0.719-3.578)</td>
<td>.249</td>
</tr>
<tr>
<td>SUD full</td>
<td>MAO</td>
<td>0.382 (0.155-0.940)</td>
<td>.036</td>
</tr>
</tbody>
</table>

Vanyukov et al. (in press) Psychiatric Genetics
MAOA & SUD

Low activity

- increase in the risk
- limbic volume reductions, hyperresponsive amygdala during emotional arousal, diminished reactivity of regulatory prefrontal regions (Meyer-Lindenberg et al., 2006)
### Drug use severity

<table>
<thead>
<tr>
<th>Trait</th>
<th>Drug Use Screening Inventory substance use problems scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>94 male Caucasian adolescents (12-18 years of age) with a DSM-IV diagnosis of Substance Dependence related to illicit drugs</td>
</tr>
<tr>
<td>Genes</td>
<td>Polymorphisms in DRD1-DRD5 genes</td>
</tr>
<tr>
<td>Analysis</td>
<td>Two-way ANOVA, testing main effects and interactions between D1- and D2-family genes</td>
</tr>
</tbody>
</table>
Interactions as expected

<table>
<thead>
<tr>
<th>Predictor sets</th>
<th>df</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD1.1</td>
<td>2</td>
<td>2.28</td>
<td>.108</td>
</tr>
<tr>
<td>DRD2</td>
<td>1</td>
<td>0.02</td>
<td>.898</td>
</tr>
<tr>
<td>DRD1.1×DRD2</td>
<td>1</td>
<td>4.39</td>
<td>.039</td>
</tr>
<tr>
<td>DRD1.1</td>
<td>2</td>
<td>3.63</td>
<td>.031</td>
</tr>
<tr>
<td>DRD3</td>
<td>4</td>
<td>1.09</td>
<td>.369</td>
</tr>
<tr>
<td>DRD1.1×DRD3</td>
<td>6</td>
<td>2.29</td>
<td>.044</td>
</tr>
<tr>
<td>DRD1.7</td>
<td>2</td>
<td>4.47</td>
<td>.015</td>
</tr>
<tr>
<td>DRD3</td>
<td>4</td>
<td>0.72</td>
<td>.584</td>
</tr>
<tr>
<td>DRD1.7×DRD3</td>
<td>6</td>
<td>2.60</td>
<td>.025</td>
</tr>
</tbody>
</table>
Candidate system genes

*Comorbidity helps:*
- multiple hits
- cross-verify
- identify pathways
- support the gene’s role
Dynamic

Note: G×E omitted
Genetic roots

... environmental “Roundup”?