Causes of variability in developmental disorders

Is the medical risk model appropriate for understanding behavioural deficits?

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Workshop: Developmental disorders: co-morbidity, subgroups and variability
Outline

• Comorbidity between disorders
  – with apparently unrelated causes

• Variability in disorders
  – even when they have a common genetic cause

• Formal models
  – to identify common causes, risk factors
Part 1: Comorbidity
Comorbidity

• An anecdote: One family in 30 million
  – A child with Williams syndrome
  – A sibling with cystic fibrosis
  – A coincidence? Very low odds...
  – A common causal factor? But what could that be?
Comorbidity

• Two disorders co-occur more frequently than would be predicted by their individual incidence

• Existing theories maintain separate causes for disorders

• Should not be a superficial resemblance

• A is the same in A alone, A+B, A+C

• Implication: common causal factor, but at what level?
Check it’s not...

• Ascertainment bias
  – SLI co-occurs with speech disorders!
  – … in clinical samples, where referral is often triggered by parents noticing the speech disorder
  – Trust population samples more

• Phenocopy / Phenomimicry
  – E.g., kids with ADHD don’t spend enough time learning to read … and end up diagnosed with comorbid reading disorder…
The rule not the exception

• Comorbidy of behaviourally defined disorders appears to be the rule not the exception

• Examples (Williams & Lind, 2013)
  – ~50% of adolescents with ADHD have conduct disorder or oppositional defiant disorder
  – 13% of ADHD have major depressive disorder, 13% have anxiety disorder
  – 50% of children/adolescents with depressive disorder have anxiety disorder
  – 70% of children with ASD have at least one other disorder (e.g., social anxiety disorder), 40% have two or more
  – 50% of children with ASD have language impairment (SLI)
  – 20-40% of children with dyslexia have ADHD (esp. inattentive subtype)
The rule not the exception

• Enough to suggest no point in DSM / ICD categories of discrete disorders?
  – Or that the existing categories are the wrong ones?

• A move to overlapping spectrums?
Theories of comorbidity

1. Independence of traits
   • E.g., Ronald et al. (2006)

2. Risk factor model
   • E.g., Bishop (2006)

3. Developmental instability
   • E.g., Yeo, Gangestad & Thoma (2007)

4. ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations)
   • E.g., Gillberg (2010)
1. Independence of traits

- Traits are inherited separately
- Traits are continuous with the normal population

- Example: ASD (Ronald et al., 2006)
  - Low genetic correlation between social skills, communication skills, restricted repertoire of interests
  - Score low on all three and you are autistic
  - Predicts lower incidence for greater combination of deficits?
Genetic Heterogeneity Between the Three Components of the Autism Spectrum: A Twin Study

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ABSTRACT

Objective: This study investigated the etiology of autistic-like traits in the general population and the etiological overlap between the three aspects of the triad of impairments (social impairments, communication impairments, restricted repetitive behaviors and interests) that together define autism spectrum disorders. Method: Parents of 3,400 8-year-old twin pairs from the Twins Early Development Study completed the Childhood Asperger Syndrome Test, a screening instrument for autism spectrum symptoms in mainstream samples. Genetic model-fitting of categorical and continuous data is reported. Results: High heritability was found for extreme autistic-like traits (0.64–0.92 for various cutoffs) and autistic-like traits as measured on a continuum (0.78–0.81), with no significant shared environmental influences. All three subscales were highly heritable but showed low covariation. In the genetic modeling, distinct genetic influences were identified for the three components. Conclusions: These results suggest the triad of impairments that define autism spectrum disorders is heterogeneous genetically. Molecular genetic research examining the three components separately may identify different causal pathways for the three components. The analyses give no indication that different genetic processes affect extreme autistic impairments and autistic impairments as measured on a continuum, but this can only be directly tested once genes are identified. J. Am. Acad. Child Adolesc. Psychiatry, 2006;45(6):681–699. Key Words: twins, genetics, autism spectrum disorders.
2. (Medical) risk model

• Bishop (2006) – causal models for developmental disorders
  – Does A cause B? If A dissociates from B, it cannot cause it
  – Issue with developmental disorders: despite dissociations, frequent associations between deficits

‘Cognitive studies of development disorders have often embraced parsimony and have looked for a single necessary and sufficient cause of disorders such as dyslexia, SLI and autism ... A “single cause” approach is too simple to account for the clinical reality. Identifying risk factors, and determining how they operate together, may be a more fruitful approach.’

(Bishop, 2006, p.1165-6)
2. (Medical) risk model

- Causes are only probabilistically related to effects
  - Example: Smoking and lung cancer
    - Cases of lung cancer without smoking, or smokers living to old age do not undermine confidence in causal relation

- Like diseases, idea is that disorders caused by accumulation of many risk factors, each of small effect
- Causes may have risks for more than one disorder

- Common causal factors identified at the genetic level (Bishop, 2010)
  - E.g., genes have risk for SLI and autism, or autism and ADHD
A Functional Genetic Link between Distinct Developmental Language Disorders


RESULTS
We found that FOXF2 binds to and dramatically down-regulates CNTNAP2, a gene that encodes a neurexin and is expressed in the developing human cortex. On analyzing CNTNAP2 polymorphisms in children with typical language impairment, we detected significant quantitative associations with nonsense-word repetition, a heritable behavioral marker of this disorder (peak association, P=5.0×10⁻⁸ at SNP rs1736239). Intriguingly, this region coincides with one associated with language delays in children with autism.
Challenges

• What’s a probabilistic cause?
  – Who throws the dice?
  – Is a risk factor model just a re-description of statistical data, dressed up as cause?

• What’s the difference between a causal factor and a risk factor?
Endophenotype

• Definition: here ... cognitive marker of a disorder
  – E.g., non-word repetition deficits in SLI

• Criteria: (Williams & Lind, 2013; Gottesman & Gould, 2003)
  – Marker is associated with disorder
  – Present at all stages of the disorder (even if some symptoms have resolved)
  – Heritable
  – Present in unaffected family members at greater levels than expected by chance

• Confusing: ‘causes’ of disorders present in unaffected siblings?
  – see also: white matter connectivity and brain size for ASD and siblings

• Are we seeing individual differences in resilience to atypicality?
3. Developmental instability

- Lots of factors introduce noise into the developmental process
- General risk factors for poor development combine with specific factors to produce separate disorders
- Explains why families can have siblings with different disorders at above chance levels
- Developmental instability can be measured by markers, including fluctuating asymmetry and minor physical anomalies

Examples:
- Fluctuating asymmetry – right vs left finger length, ear length
- Minor physical anomalies – wide-spaced eyes

Developmental Instability and Individual Variation in Brain Development
Implications for the Origin of Neurodevelopmental Disorders
Ronald A. Yeo, Steven W. Gangestad, and Robert J. Thomas
Greater DI correlates with atypical functional brain asymmetry

Values show right-minus-left latency
Peter Hammond: 3d imaging of face morphology

(Hammond et al., 2007)
Face-brain asymmetry in autism spectrum disorders.


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Abstract
The heterogeneity of autism spectrum disorders (ASDs) confounds attempts to identify causes and pathogenesis. Identifiable endophenotypes and reliable biomarkers within ASDs would help to focus molecular research and uncover genetic causes and developmental mechanisms. We used dense surface-modelling techniques to compare the facial morphology of 72 boys with ASD and 128 first-degree relatives to that of 254 unrelated controls. Pattern-matching algorithms were able to discriminate between the faces of ASD boys and those of matched controls (AUC=0.82) and also discriminate between the faces of unaffected mothers of ASD children and matched female controls (AUC=0.76). We detected significant facial asymmetry in boys with ASD (P<0.01), notably depth-wise in the supra- and periorbital regions anterior to the frontal pole of the right hemisphere of the brain. Unaffected mothers of children with ASD display similar significant facial asymmetry, more exaggerated than that in matched controls (P<0.03) and, in particular, show vertical asymmetry of the periorbital region. Unaffected fathers of children with ASD did not show facial asymmetry to a significant degree compared to controls. Two thirds of unaffected male siblings tested were classified unseen as more facially similar to unrelated boys with ASD than to unrelated controls. These unaffected male siblings and two small groups of girls with ASD and female siblings, all show overall directional asymmetry, but without achieving statistical significance in two-tailed t-tests of individual asymmetry of ASD family and matched control groups. We conclude that previously identified right dominant asymmetry of the frontal poles of boys with ASD could explain their facial asymmetry through the direct effect of brain growth. The atypical facial asymmetry of unaffected mothers of children with ASD requires further brain studies before the same explanation can be proposed. An alternative explanation, not mutually exclusive, is a simultaneous and parallel action on face and brain growth by genetic factors. Both possibilities suggest the need for coordinated face and brain studies on ASD probands and their first-degree relatives, especially on unaffected mothers, given that their unusual facial asymmetry suggests an ASD susceptibility arising from maternal genes.

PMID: 18317467 [PubMed - indexed for MEDLINE]
3. Developmental instability

- Predictions:
  - More common disorders require fewer additional specific factors and will more directly result from DI
  - Affected individuals relatively low in DI may be most revealing of specific genetic influences or brain abnormalities

- Biological development can go wrong for multiple reasons, some of these predict generally poor outcome
4. ESSENCE

• Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (Gillberg, 2010)

‘Co-existence of disorders – including attention-deficit/hyperactivity disorder, oppositional defiant disorder, tic disorder, developmental coordination disorder, and autism spectrum disorder – and sharing of symptoms across disorders (sometimes referred to as comorbidity) is the rule rather than the exception in child psychiatry and developmental medicine . . . Major problems in at least one ESSENCE domain before age 5 years often signals major problems in the same or overlapping domains years later. There is no time to wait; something needs to be done, and that something is unlikely to be just in the area of speech and language, just in the area of autism or just in special education.’ (Gillberg, 2010, p. 1543)

• View shaped by clinical experience

• Implies discrete disorders created by diagnostic categories
4. ESSENCE

• Most referrals occur because there is more than one deficit

• Single behavioural deficits are on continuum with population variation, and not enough for disorder diagnosis

• Two or more disorders trigger referral
  – E.g., autism and learning disability

• Early on, disorders overlap
  – E.g., diagnostic symptoms for autism and ADHD

• Early referral implies ‘something bad this way comes’

• Gender differences in disorders may be referral bias
Disorders may be shared only by 4 or 5 kids in the world
Similarity is enforced by need to diagnose

Clinical view doesn’t address mechanistic basis for differential outcome and/or co morbidty
  – Why do certain neural systems tend to be developmentally impaired together?
The importance of levels

• Where is the common causal factor in comorbid disorders?
  – Replication?
  – Genetic
  – Neurobiological
  – Cognitive
  – Behavioural

At what level(s) of explanation [do disorders] need to overlap in order for them to be considered comorbid, and what evidence can be used to establish such comorbidity (or lack thereof)?

We suspect that in the coming years, molecular genetic studies will reveal many “generalist” genes that contribute to multiple disorders ... Ultimately, however, our concern is whether our understanding of each disorder is best served by focusing on “comorbidity” at this level of analysis. In order to understand developmental disorders (and have realistic hope of remediating them), we require an understanding of the causal chain between genes and behaviour, via neurobiology and cognition ... Perhaps therefore, only when “comorbid” disorders share similar causal pathways will a focus on comorbidity lead to successful remediation of both disorders.

Williams & Lind (2013):
Best level is the one that helps remediation
The importance of time

- Associations may change over development
  - Must A and B must co-exist to be comorbid, and rule out that A caused B?

- Deficit spread and compensation likely in interactive systems

  - 2-3 social skills do not predict morphosyntax at 4-5 but they do at 10-11 (spread)
  - 2-3 nonword rep. skills predict morphosyntax at 4-5 but they do not at 10-11 (compensation)
The importance of time

A differentiating developmental process...
The importance of time

A differentiating developmental process...
The importance of time

A differentiating developmental process...
The importance of time

A differentiating developmental process...
Partial causal overlap

• Example 1: ASD and (S)LI
  – Nonword repetition deficit is of different character in ASD+LI (delay) and SLI (deviant) (Riches et al., 2010)
  – Qualitatively different pattern of tense marking deficits for LI on own or with ASD (Williams et al., 2008)
  – Behavioural similarity, cognitive _dissimilarity_, but genetic overlap?

• Example 2: ADHD and dyslexia
  – Test battery + SEM (McGrath et al., 2011)
  – Inhibition uniquely related to ADHD
  – Phonological awareness uniquely related to dyslexia (reading)
  – Processing speed related to both dyslexia and ADHD (esp. inattentive measures)
Part 2: Variability
Variability

• Issues:
  – Different forms of variation:
    • Genetic disorders vs behaviourally defined disorders vs normal population variation
  – Genetic disorders vary in severity
    • Caused by what?
  – Are behavioural disorders single disorders, despite the variability?
  – Can qualitatively different disorders be generated by a causal continuum?
Variability in genetic disorders

• Possibilities:
  – A single disorder interacts with population wide individual variability
    • E.g., in DS mouse, triplicated genetic material altered gene expression in over 200 other genes, including on other chromosomes; those other genes might vary...
  – The disorder itself varies
    • E.g., in deletion/duplication size
    • E.g., genes on the other chromosome varies

• Genetic disorders may have single cause but gene-behaviour relation is not deterministic
Cooper et al. (2011): A copy number variation morbidity map of developmental delay

To understand the genetic heterogeneity underlying developmental delay, we compared copy number variants (CNVs) in 15,767 children with intellectual disability and various congenital defects (cases) to CNVs in 8,329 unaffected adult controls.

We estimate that ~14.2% of disease in these children is caused by CNVs >400 kb.

We observed a greater enrichment of CNVs in individuals with craniofacial anomalies and cardiovascular defects compared to those with epilepsy or autism.

Mutations / deletions often appear in unaffected controls as well as disorder group...
Disorder vs TD variation

• Is variability greater in the disorder than typical development?
  – Example: cochlear implants and language development (Szagun, 2012)
  – Very variable subsequent language development
  – More variability explained by family language environment than timing of implant (all < 4 years)
  – Most variance left unexplained
  – To do with child-specific variable success of physical connection of implant to neural tissue (unmeasurable?)

• Behavioural disorders sometimes compress variation (by definition)
  – If you select a group via a particular criterial behaviour, the variability on that behaviour will be small
The double hit

- Disorder needs a double hit, otherwise it’s just variation in the normal population
  - Idea in Independent Traits / DI / ESSENCE frameworks

- A disorder is cleaving a spectrum
- The cleave lands at the double hit

- Variability and comorbidity are linked
Part 3: Formal models
Formal models

• Bishop (2010)
  – Genetic explanation of comorbidity of ASD and LI

• Thomas (2003)
  – Single-cause vs. multiple-cause disorder groups can be distinguished by cross-measure variability

• Thomas, Knowland & Karmiloff-Smith (2011)
  – Autism and developmental regression – probabilistic causes, risk and protective factors

• Thomas (unpublished data)
  – Does sibling cognitive ability predict autism severity?

• Thomas & Knowland (in prep.)
  – Sub-groups in early language delay – when does delay resolve versus persist? Why does delay sometimes have late onset?
Bishop (2010)

• Statistical model that generates population-level MZ and DZ behavioural scores from genotypes + assumptions about environment
  – No developmental process, no actual behaviour, environmental influence is shared noise or unique noise

• Key data to explain:
  – Relative incidence of pure SLI, pure ASD, and ASD+LI
  – Parents and siblings of children with SLI more likely to have language deficits than average (LI heritable)
  – Parents and siblings of children with ASD+LI not more likely to have language deficits than average (LI not heritable)
  – A variant of the gene CNTNAP2 occurs more frequently than expected in individuals with ASD and in individuals with SLI
Fig. 6 Correlated risks with epistasis model. The shield-shaped symbol depicts an AND gate, whereby there is an extra impact on the language trait only if both risk factors X and Y are present.

Table 1 Results from correlated risks with epistasis simulation, with 10 genes, one of which is pleiotropic. The effect of the pleiotropic gene is magnified by risk genotypes from ASD genes (see text)

<table>
<thead>
<tr>
<th>Proband diagnosis</th>
<th>None</th>
<th>SLI</th>
<th>ASD</th>
<th>ASD+LI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (%)</td>
<td>92.14</td>
<td>6.20</td>
<td>0.98</td>
<td>0.67</td>
</tr>
<tr>
<td>Percentage relatives with pure LI</td>
<td>5.11</td>
<td>21.59</td>
<td>6.01</td>
<td>13.80</td>
</tr>
<tr>
<td>Percentage relatives with pure ASD</td>
<td>0.89</td>
<td>0.74</td>
<td>8.35</td>
<td>5.19</td>
</tr>
<tr>
<td>Percentage relatives with ASD+LI</td>
<td>0.52</td>
<td>1.53</td>
<td>4.58</td>
<td>8.75</td>
</tr>
<tr>
<td>LI trait mean in probands</td>
<td>0.15</td>
<td>-1.93</td>
<td>-0.53</td>
<td>-2.37</td>
</tr>
<tr>
<td>ASD trait mean in probands</td>
<td>0.07</td>
<td>-0.31</td>
<td>-2.74</td>
<td>-3.09</td>
</tr>
<tr>
<td>LI trait mean in relatives(^a)</td>
<td>0.08</td>
<td>-0.81</td>
<td>0.05</td>
<td>-0.53</td>
</tr>
<tr>
<td>ASD trait mean in relatives(^a)</td>
<td>0.07</td>
<td>-0.07</td>
<td>-0.83</td>
<td>-0.84</td>
</tr>
</tbody>
</table>

\(^a\) Excluding relatives with ASD liability score below cutoff
Comorbidity model

LI risk genes  ASD risk genes

SLI  ASD+LI

CNTNAP2
Thomas (2003)

Simple artificial neural network learning models with atypical parameters

Study 1

Study 2
Thomas (2003)

• Two groups of learning systems
  – One has have single underlying processing deficit (+ individual variability) - **homogeneous**
  – Second has individuals with different underlying processing deficits (+ individual variability) – **heterogeneous**

• Disorder defined according to one behaviour, five other behaviours also measured

• Question:
  – Can the homogeneous disorder group be distinguished from the heterogeneous group based on behaviour alone?

• Answer:
  – Yes, for the homogeneous group, variability is about the same across all measures; for heterogeneous group, variability is smallest on definitional (criterial) measure, increases on other measures
  – Prediction illustrated with data on word finding, comparing Williams syndrome group (**homogeneous**) with behaviourally defined (**heterogeneous**) group
Thomas, Knowland & Karmiloff-Smith (2011)

• Model of developmental regression in autism

• Consideration of:
  – causal vs. risk factors
  – variability in regression severity and recovery
  – links between regression and wider ASD phenotype
Population modelling framework

Variability in genome

Variability in environmental input

Developmental process
Basic model assumes variation in many neurocomputational parameters

- Nearest neighbour threshold
- Weight decay
- Steepness of sigmoid threshold
- Number of internal units
- Weight change learning rate
- Weight change momentum
- Learning algorithm error metric
- Pruning: i. onset ii. threshold iii. probability
- Architecture (2-layer, 3-layer, fully connected)
- Transmission noise
- Variance of initial random weight sizes
- Sparseness of initial connectivity
Human brain initially produces surplus neurocomputational resources (to give flexibility to environmental conditions) then prunes away unused resources to save on metabolic costs.

(data from Huttenlocher & Dabhokar, 1997)
Pruning
Pruning
Hypothesis:
Cause of behavioural regression is Aggressive Pruning
Aggressive Pruning
Aggressive Pruning
Recovery by strengthening connections that are left
Aggressive Pruning
Recovery by strengthening connections that are left
Aggressive Pruning
Recovery by strengthening connections that are left
Perhaps not enough resources to generate normal-looking behaviour
Example of typical development

Developmental profile: Individual #217
(pruning threshold = 0.4)
Example of regression, generated by altering pruning threshold parameter to allow elimination of stronger connection weights.

**Developmental profile: Individual #41**

(pruning threshold = 1.5)
In this model, any developmental factor that alters the rate at which connections are strengthened will modulate their **risk** of being pruned.

**Hypothesis:**

**Aggressive Pruning**

Includes rate of development, richness of environment

E.g., very deprived environment means small connections – raised risk for damaging pruning
Relationship between regression cause (pruning parameter) and behavioural phenotype

The pruning parameter is “the” cause of regression yet it acts probabilistically!
Stepwise logistic regression for neurocomputational parameters that modulate the **probability of showing regression** in (high-risk) population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>-2 Log likelihood</th>
<th>Nagelkerke $R^2$ change</th>
<th>Significance of model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAUSAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruning Threshold</td>
<td>734.8</td>
<td>.597</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unit threshold function</td>
<td>642.2</td>
<td>.068</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Architecture</td>
<td>624.9</td>
<td>.012</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pruning Probability</td>
<td>611.2</td>
<td>.010</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>RISK</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hidden unit number</td>
<td>603.7</td>
<td>.005</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sparseness</td>
<td>598.9</td>
<td>.003</td>
<td>.029</td>
</tr>
<tr>
<td>Momentum</td>
<td>594.8</td>
<td>.003</td>
<td>.042</td>
</tr>
<tr>
<td>*Family quotient (environment)</td>
<td>-</td>
<td>-</td>
<td>.593</td>
</tr>
</tbody>
</table>
Predictors of the **rate of development** in the normal (low-risk) population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$R^2$ change</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruning Threshold</td>
<td>.003</td>
<td>.014</td>
</tr>
<tr>
<td>Unit threshold function</td>
<td>.057</td>
<td>&lt;.001</td>
</tr>
<tr>
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<td>.055</td>
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</tr>
<tr>
<td>Hidden unit number</td>
<td>.018</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sparseness</td>
<td>.008</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Momentum</td>
<td>.028</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Family quotient (environment)</td>
<td>.023</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Link overt regression to wider phenotype by variations in the onset of pruning

- Autism
- Autism + behavioural regression
- Childhood Disintegrative disorder

Slower development would make autism rather than the autism+regression more likely
Genetic account in this model

• Regression caused by either
  – Mild pruning threshold + accumulation of population wide risk factors (continuum)
  or
  – Mutation causes unusually high pruning threshold (discrete)

• Comorbidity of regression and delay occur because causes of delay are risk factors for regression
  – For Bishop (2010) comorbidity arises at genetic level
  – Here comorbidity occurs at a neurocomputational level
Does sibling ability predict regression severity in affected network?
- Sibling ability = population rank
- Regression severity = size of drop in performance

Results
- Weak effects
- Sibling rank predicted 8% of variation in severity (p=.018)
- Simulations allowed investigation of individuals who you would expect to show regression but did not (clinically invisible)
- Low ability provided protection against regression (high ability = risk)
• Early diagnosed language delay sometimes persists, sometimes resolves – are these qualitatively different subgroups?
• Some delay is late onset – what is the cause?

• Population demonstrated
  – Resolving delay
  – Persisting delay
  – Late onset

• Resolving and persisting delay were on continuum
  – determined by computational dimensions of plasticity and capacity
• Late onset combined two groups:
  – (1) late development limited by poor environment
  – (2) late regressive events reduced capacity
Summary of formal models

• Population-level modelling
  – Specify genetic, neurocomputational, environmental variables
  – Simulate developmental process
  – Genetic level allows investigation of heritability

• It allows you to
  – consider hypotheses that stipulate interaction of causal and risk factors
  – examine the mechanistic basis of variability
    • Probabilistic cause = presence of protective factors
  – test hypotheses on the specificity of factors, and the overlap between disorders
  – investigate subgroups
  – investigate common causal pathways
Conclusions
Overall conclusions

- ‘Probabilistic cause’, ‘risk/protective factors’ increasingly influential ideas
- Idea of double / triple hit
- Comorbidity the norm – perhaps disorder categories are wrong
- Non-specificity of early poor development?
- Importance of detailed phenotyping (specific and sensitive)

- Dispute about level of common causal factors that makes it worth calling co-occurrence ‘comorbidity’
  - behaviour too high, genetics too low, cognition just right?
  - Which level is most use for remediation? Common cause implies common remediation...

- Sources of variability not well understood, especially typical versus atypical variability
- Formal models required to formulate hypotheses about outcomes with complex developmental causes
• Annette Karmiloff-Smith
• Victoria Knowland
• Neil Forrester
• Tony Charman
• Mark Johnson
• Members of the DNL
• Susan Golden-Meadow
• Susan Levine