Troubled by Heterogeneity?

Opportunities for Fresh Views on Long–standing and Recent Issues in Biology and Biomedicine

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Troubled by Heterogeneity!

Audience = mix of:
  - Theoretical biologists
  - Philosophers of science
  - Historians & sociologists of science
  - Life scientists
  - Policy makers
Prologue

troubling environmental studies with heterogeneity
two islands
two islands

70% of population

2% of population
analysis of causes & implications of the analysis

change qualitatively if uniform units are replaced by unequal units that are subject to further differentiation as a result of their linked economic, social & political dynamics
Unruly Complexity (U. Chicago Press, 2005)

= situations (in ecology & STS & teaching)

1. heterogeneous components
2. built up over time & subject to ongoing restructuring
3. embedded in wider dynamics
Unruly complexity in ecology →

Complexities of biosocial development
(especially social epidemiology)
Unruly complexity in ecology ->

Complexities of biosocial development (especially social epidemiology) ->

Un/troubled by Heterogeneity?
Application of human heritability if “underlying heterogeneity” is possible?
Heritability

e.g. Heritability of IQ is 60–80% meaning?
Heritability

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meaning?

• genes have more influence on IQ than environment?
Heritability

e.g. Heritability of IQ is 60–80%

meaning?

• genes have more influence on IQ than environment?
• changing genes has more influence on IQ than changing environment?
Heritability

e.g. Heritability of IQ is 60–80%

meaning?

- genes have more influence on IQ than environment?
- changing genes has more influence on IQ than changing environment?
- variation among means of genetic varieties (averaged across all locations) > variation of means of locations (averaged over all varieties)
underlying heterogeneity = 
hetereogeneity of genetic & environmental 
factors underlying development of trait
Application of human heritability if underlying heterogeneity is possible?
Application of human heritability if underlying heterogeneity is possible??

- Undertake research w/o reference to trait’s heritability
- Use high heritability => trait is potentially worthwhile candidate for molecular research
- Restrict attention to variation within a set of relatives
- Focus on heritability as a fraction of the variation (useful in ag. & lab. breeding)
- Restrict range of varieties or locations
Underlying heterogeneity not (yet) recognized as significant
Underlying heterogeneity
not recognized as significant

→ deeper social/historical & conceptual roots?

→ opportunities for fresh views on long-standing & recent issues in biology & biomedicine?
Conceptual: from typological thinking to recognizing possible underlying heterogeneity
From typological thinking to recognizing possible underlying heterogeneity
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From typological thinking to recognizing possible underlying heterogeneity

Q: Why treat observations this way?
From typological thinking to recognizing possible underlying heterogeneity

spread of values for group A in location a

spread of values for group B in location b
From typological thinking to recognizing possible underlying heterogeneity
spread of values for group A in location a

spread of values for group B in location b

genetic factors for groups A & B

environmental factors for groups in locations a & b
From typological thinking to recognizing possible underlying heterogeneity
Q: How to expose these factors?
Social–historical underpinnings:

heterogeneity–control–infrastructure–participation

mean group A in location a
mean group B in location b

gfs
efs
Social-historical underpinnings:

heterogeneity-control-infrastructure-participation
lematic early in life, because there is insufficient MAOB (a homolog of MAOA with broad specificity to neurotransmitter amines) to compensate for an MAOA deficiency (8).

Based on the hypothesis that MAOA genotype can moderate the influence of childhood maltreatment on neural systems implicated in antisocial behavior, we tested whether antisocial behavior would be predicted by an interaction between a gene (MAOA) and an environment (maltreatment). A well-characterized variable number tandem repeat (VNTR) polymorphism exists at the promoter of the MAOA gene, which is known to affect expression. We genotyped this polymorphism in members of the Dunedin Multidisciplinary Health and Development Study, a sample without population stratification confounds (27). This birth cohort of 1,037 children (52% male) has been assessed at ages 3, 5, 7, 9, 11, 13, 15, 18, and 21 and was virtually intact (96%) at age 26 years.

The study offers three advantages for testing gene-environment (G × E) interactions. First, in contrast to studies of adjudicated or clinical samples, this study of a representative general population sample avoids potential distortions in association between variables (28, 29). Second, the sample has well-characterized environmental adversity histories. Between the ages of 3 and 11 years, 8% of the study children experienced “severe” maltreatment, 28% experienced “probable” maltreatment, and 64% experienced no maltreatment (27). (Maltreatment groups did not differ on MAOA activity, χ²(2) = 0.38, P = 0.82, suggesting that genotype did not influence exposure to maltreatment.) Third, the study has ascertained antisocial outcomes rigorously. Antisocial behavior is a complicated phenotype, and each method and data source used to measure it (e.g., clinical diagnoses, personality checklists, official conviction records) is characterized by different strengths and limitations. Using information from independent sources appropriate to different stages of development, we examined four outcome measures (27). Adolescent conduct disorder was assessed according to criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); convictions for violent crimes were identified via the Australian and New Zealand police; a personality disposition toward violence was measured as part of a psychological assessment at age 26; symptoms of antisocial personality disorder were ascertained at age 26 by collecting information about the study members from people they nominated as “someone who knows you well.” A common-factor model fitted the four measures of antisocial behavior well (27), with factor loadings ranging from 0.64 to 0.74, showing that all four measures index liability to antisocial behavior.

Using moderated regression analysis, we predicted scores on a composite antisocial index comprising the four measures of antisocial behavior (27) (Fig. 1). The main effect of MAOA activity on the composite index of
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Fig. 1. Means on the composite index of antisocial behavior as a function of MAOA activity and a childhood history of maltreatment (27). MAOA activity is the gene expression level associated with allele variants of the functional promoter polymorphism, grouped into low and high activity; childhood maltreatment is grouped into 3 categories of increasing severity. The antisocial behavior composite is standardized (z score) to M = 0 and SD = 1; group differences are interpretable in SD unit differences (d).

Fig. 2. The association between childhood maltreatment and subsequent antisocial behavior as a function of MAOA activity. (A) Percentage of males (and standard errors) meeting diagnostic criteria for Conduct Disorder between ages 10 and 18. In a hierarchical logistic regression model, the interaction between maltreatment and MAOA activity was in the predicted direction, b = −0.63, SE = 0.33, z = 1.87, P = 0.06. Probing the interaction within each genotype group showed that the effect of maltreatment was highly significant in the low–MAOA activity group (b = 0.96, SE = 0.27, z = 3.55, P < 0.001), and marginally significant in the high–MAOA group (b = 0.34, SE = 0.20, z = 1.72, P = 0.09). (B) Percentage of males convicted of a violent crime by age 26. The G × E interaction was in the predicted direction, b = −0.83, SE = 0.42, z = 1.95, P = 0.05. Probing the interaction, the effect of maltreatment was significant in the low–MAOA activity group (b = 1.20, SE = 0.33, z = 3.65, P < 0.001), but was not significant in the high MAOA group (b = 0.37, SE = 0.27, z = 1.38, P = 0.17). (C) Mean z scores (M = 0, SD = 1) on the Disposition Toward Violence scale at age 26. In a hierarchical ordinary least squares (OLS) regression model, the G × E interaction was in the predicted direction (b = −0.24, SE = 0.15, t = −1.62, P = 0.10); the effect of maltreatment was significant in the low–MAOA activity group (b = 0.35, SE = 0.11, t = 3.09, P = 0.002) but not in the high MAOA group (b = 0.12, SE = 0.07, t = 1.34, P = 0.17). (D) Mean z scores (M = 0, SD = 1) on the Antisocial Personality Disorder symptom scale at age 26. The G × E interaction was in the predicted direction (b = −0.31, SE = 0.15, t = −2.02, P = 0.04); the effect of maltreatment was significant in the low–MAOA activity group (b = 0.45, SE = 0.12, t = 3.83, P < 0.001) but not in the high MAOA group (b = 0.14, SE = 0.09, t = 1.57, P = 0.12).
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A, B = genetic condition
1, 2 = envtl. condition/
medical treatment
PKU
people
diagnosis

care

social support

infant

neonatal

1960

1966

1970

1980

1990

2000

90% newborns tested
diet

other

1974

1984

NAR

MRS

referral

overcome

PKUCS

study

1967 PKUCS

assessment of

C/B

simplest test added

causal

open up this period

(Story more interesting than diagram)

P71

PKU people

PKU condition

diagnosis

care

neonatal diet

hard to maintain

improved

improvements

low IQ & other deficits

drug therapy

social support

mandated

subsidy

religion

ethnic

medical social psychological

medical social psychological services

0

1/6

teenager

young adulthood
Anxious attachment → childhood helplessness & low self-esteem → current helplessness → hopeless depression → severe event

Loss of mother → lack of care → institution

Continuing working class → chronically difficult living conditions

Premarital pregnancy

Hypothetical genetics/biochemistry

* = point of possible intervention

Time
Troubled by Heterogeneity?

Theoretical biologists?
Philosophers of science?
Historians & sociologists of sci.?
Life scientists?
Policy makers?
research and application of resulting knowledge

not troubled by variation, particularity, heterogeneity

to the extent that populations are well controlled

established and maintained through considerable effort or social infrastructure

pay more attention to possibilities for participation

inviting more attention to