One or Many Schizophrenias

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Introduction

- Conceptual status of schizophrenia – one or many diseases – long debated
  - Bleuler 1911, *Dementia or the Group of Schizophrenias*

- Thought experiment: different answers depending on language game (Wittgenstein) or framework in which question is posed

- Three frameworks:
  - Biomedical framework
    - DSM/ICD
  - Dimensional framework
    - DSM changes
  - Genetic framework
    - GWAS (Genome Wide Association Studies)
I. Schizophrenia in a Biomedical Framework


- DSM-III in fact represents the biomedical model
  - Follows ICD, psychiatric illnesses as subgroup of medical illnesses.
  - DSM-III as elaboration of ICD mental health section
  - Reliance on subjective symptoms as indication of underlying illness

- Reliance on subjective symptoms raises issues of reliability and validity
  - Reliability – consensus in making diagnosis
  - Validity – diagnosis reflects real-world psychopathology

- Failure to achieve validity associated with multiple problems
  - *A Research Agenda*, 2002. “In more than 30 years since the introduction of the Feighner criteria by Robins and Guze, which eventually led to DSM-III, the goal of validating these syndromes and discovering common etiologies has remained elusive.”
Schizophrenia in a Biomedical Framework

- Failures of biomedical, categorical model:
  - Heterogeneous phenotypes
  - Fuzzy boundaries and overlapping diagnoses
  - Varied course of illness and outcome
  - No common response to treatment, pharmacologic and rehabilitative
  - No common etiology
  - No biomarker after 100 years of research

- Conclusion: biomedical, categorical model supports argument of schizophrenia as multitude of variously related disorders
II. Schizophrenia in a Dimensional Framework

- Grouping schizophrenia across the DSMs
  - DSM-5: Schizophrenia Spectrum and Other Psychotic Disorders
- Increased recognition of limitations of categorical system
  - Categorical: patient does or does not have the condition
  - “Structural problems rooted in the basic design of the previous DSM classification, constructed of a large number of narrow diagnostic categories, have emerged in both clinical practice and research”
- New DSM-5 measure: “Clinician-rated dimensions of psychosis symptom severity”
  - Dimension only refers to symptom, not diagnosis itself
II. Schizophrenia in a Dimensional Framework

- Failure to make the diagnosis itself dimensional
- Making diagnosis dimensional would result in a fully dimensional model

- Conclusion: a fully dimensional model could uphold schizophrenia as a unitary diagnosis with degrees of severity
III. Schizophrenia in a Genetic Framework

- Biomedical framework → many schizophrenias
- Dimensional framework → one schizophrenia
- Genetic framework → both?? Other??
III. Schizophrenia in a Genetic Framework

- High heritability in schizophrenia
- But no Mendelian gene for schizophrenia
- Schizophrenia as genetically complex disorder
- Failure of linkage studies
- Discovery of the human genome and Genome Wide Association Studies (GWAS)
III. Genome-wide Association Studies

GWAS

- Schizophrenia a polygenic condition
- Each risk gene of low effect size, but in combination with others associated with risk of schizophrenia
- Given modest effect size of each risk gene, very large samples required for associations to be made
- Collectively estimated to account for $\frac{1}{3} - \frac{1}{2}$ of genetic liability
III. Genome-wide Association Studies (GWAS)

- Psychiatric Genomics Consortium GWA study
- 36,989 schizophrenia cases and 113,075 controls from more than 80 research institutions and groups
- 128 independent associations from 108 genomic loci, 83 not reported previously
III. Genome-wide Association Studies

Issues

- Definite disease pathways not yet clear
- Schizophrenia risk genes involve other conditions like intellectual disability and autism
- Genetic risk loci do not cover full etiology of schizophrenia
III. Genome-wide Association Studies
One-or-many question: 2 answers

1. First answer

- GWA studies assume biomedical model in choosing subjects and finding pathways confirming model

- Conclusion: schizophrenia as unitary condition with polygenic etiology and heterogeneous phenotypes
III. Genome-wide Association Studies
One-or-many question: 2 answers

2. Second answer: with multiple risk loci...
   - Associations of schizophrenia and other psychiatric conditions
   - Pathway to dimensional framework??
   - Pathway to powerful phenotype? Unique disorder? (cont.)
III. Genome-wide Association Studies
One-or-many question: 2 answers

2. Second answer: with multiple risk loci...

- Old Robins/Guze distinction between good and bad outcome schizophrenia
- Shuffle the deck: find any pathway leading anywhere – even to presentations not usually thought of as schizophrenic
III. Genome-wide Association Studies

One-or-many question

Conclusion

Given that the GWA studies can probably support any view of schizophrenia – as one, or as many and varied and different – we have to conclude that, from the genetic framework, the one-or-many question is unanswerable.
“All of us carry schizophrenia risk variants, and the vast majority of us carry quite a lot of them. With respect to genetic risk, there is no ‘them’ and ‘us,’ only subtle shades of gray.” … Kenneth Kendler