Schizophrenia Recent Advances

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What is schizophrenia?

- Common (1%) severe psychiatric disorder
  - Onset typically in early adulthood

- “Psychotic” disorder
  - Positive symptoms
  - Negative symptoms
  - Cognitive impairment

- A very complex phenotype with many aspects of brain function affected

- A syndrome or collection of syndromes
  - Very clinically heterogeneous
  - Schizophrenia spectrum exists

- Pathophysiology unknown

- Neurodevelopmental component
  - Epidemiology
  - Childhood abnormalities
  - Early brain changes

Bryan Charnley (1949-1991)
Genetic epidemiology proves important role for genes in schizophrenia

- ~10% risk in first degree relatives
- Heritability ($h^2$) 0.65-0.80
- Non-genetic factors also important
  – maternal malnourishment, birth complications, severe childhood abuse.
Other risk factors…

In-utero:
- Genetic
- Nutrition
- Infection

Childhood:
- Developmental delay
- Not parental upbringing
- Life Stresses/Abuse

Birth:
- Complications
- Season of birth

Adolescence & adulthood:
- Cognitive ability
- Social relationship deficits
- Cannabis use
The Stress-Vulnerability Model: Gene x Environment interplay

- Full blown disorder
- Spectrum conditions
- Asymptomatic
Mainstay of pharmacotherapy are antipsychotic drugs

- Antipsychotic drugs are dopamine antagonists and used in schizophrenia and bipolar disorder.
- Not always effective.
- Unwanted effects:
  - Don’t help cognitive and negative symptoms.
  - Efficacy related to blockade of Dopamine D2 receptor (DRD2).
- Psychosis associated with hyperdopaminergic state.
- Amphetamines can induce psychosis especially in those at high risk of SZ.

No fundamental advances in drug treatment in psychiatry in over 40 years.

Barriers to developing new treatments

- We don’t understand fundamental disease mechanisms and causes (pathogenesis)

No fundamental advances in drug treatment in psychiatry in over 40 years

- Diagnostic groups are poorly defined

Pathogenesis?

Diagnosis?
Risk genes offer route to new treatments given high heritability

Neuroscience and Epidemiology

Risk genes ➔ Mechanisms, Targets, Biomarkers

Mechanisms, Targets, Biomarkers ➔ Risk genes
Genomics

• Technology and reagents allow
  
  – **Genome-wide association studies** (GWAs): systematic search for common alleles (**SNPs**)
  
  – Genome-wide detection of sub-microscopic chromosomal abnormalities – deletions and duplications (**CNVs**)

• Whole exome sequencing underway: search for rare risk alleles in genes (**SNVs**, **indels**)

• Whole genome sequencing.
The x-axis is the allele frequency (AF) in controls. The y-axis is odds ratio. For clarity, confidence intervals are not shown. Structural variants associated with SCZ are shown as light blue diamonds. Common variants have been associated with SCZ & are shown as red diamonds.
What do genetic findings tell us about the biology?
Convergence on synaptic mechanisms

Hall et al Biological Psychiatry 2014

Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder

De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia

De novo mutations in schizophrenia implicate synaptic networks

A polygenic burden of rare disruptive mutations in schizophrenia

Biological insights from 108 schizophrenia-associated genetic loci
Risk genes offer route to new treatments

Neuroscience/Epidemiology

Models
Targets
Biomarkers

Risk genes

[Diagram with brain, mouse, and tissue samples]

[Flowchart with arrows connecting Risk genes to Models, Targets, and Biomarkers]
Current psychiatric classification (DSM/ICD)

- Syndromic, largely descriptive.
- Reliability at the expense of validity.
- Too broad and too narrow.
- Failure to map risk factors or mechanisms onto diagnoses.
Schizophrenia associated CNVs confer risk to a range of neurodevelopmental disorders
<table>
<thead>
<tr>
<th>Clinical Comorbidity</th>
<th>ID</th>
<th>ASD</th>
<th>SCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- lower IQ</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>- executive function</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>- sensorimotor gating</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Social impairment</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Communication deficit</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Repetitive behavior</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- delusions</td>
<td>Difficult</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>- hallucinations</td>
<td>Difficult</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Negative symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- asocial</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>- amotivation</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>- anhedonia</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>- alogia</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

*Shading → defining criteria. +++ highly prevalent, ++ common, + can occur*
Genes operate across our current diagnostic categories

Common alleles (polygenes)

Rare alleles (CNVs and SNVs)

Mental retardation  Autism  ADHD  Schizophrenia  Bipolar disorder

- Increasing evidence for familial overlap
- Clinical similarities
  - Impairments of cognition (general and specific)
  - Impaired social cognition
  - Developmental delay, neurological soft signs, motor abnormalities
  - Intrauterine and perinatal risk factors
- Significant co-morbidity
  - Ignored, masked by diagnostic and clinical practice

ADHD, attention deficit hyperactivity disorder; CNVs, copy number variants

PREGNANCY EXPERIENCE AND THE DEVELOPMENT OF BEHAVIOR DISORDER IN CHILDREN

BENJAMIN PASAMANICK

MARTHA E. ROGERS

ABRAHAM M. LILIENFELD

A hypothesis of a continuum of reproductive casualty is formulated consisting of brain damage incurred during these periods leading to a gradient of injury extending from fetal and neonatal death through cerebral palsy, epilepsy, mental deficiency, and behavior disorder. The implications of this continuum are discussed with regard to further research in the etiology, diagnosis, management, and prevention of these neuropsychiatric disorders.
Figure 2. Hypothesized Relationship between Current Diagnostic Categories, Extent of Neurodevelopmental Impairment and Associated Cognitive Dysfunction, Symptoms, and Various Risk Factors

Owen, Neuron, 2014.
Limitations of diagnostic categories for research

- Current categorical approaches do not appear to have biological validity and are impeding progress in research.

- Clinical neuroscience should increasingly focus on domains of psychopathology and relevant endophenotypes and not diagnoses.

- RDoC (NIMH)
Implications for psychiatric practice

• Psychiatric disorders are best conceived of as complex syndromes that lie on an causal (neurodevelopmental) as well as a symptomatic continuum.

• We are not in a position to jettison current diagnostic criteria from the clinic and replace them with a new neuroscience based approach.

• We tend to treat symptoms rather than diagnoses and should not be afraid of this.

• Categorical diagnoses are likely to remain useful to inform management, prognosis, service planning and billing but there will be an increasing shift towards dimensional as well as categorical entities.

• Evidence of continuities between childhood and adult psychiatric disorders and suggest that greater communication and continuity between child and adult services is required.
CMA now routine first-line test for Autism and Intellectual Disability (10-20% cases have clinically relevant deletion or duplication).

It is now time to consider CMA for schizophrenia (>5%).

Results will impact on physical and mental health care. Genetic counselling (50% risk on offspring).
What will diagnosis look like for the next generation of psychiatrists?

- Increasingly individualised
- Multidimensional (syndromic/symptomatic)
- Multilevel (neurobiological/aetiological).
- Implications for training
Myocardial Infarction

Diagnosis is multilevel
- MI (ECG, Enzymes)
- 3 vessel disease (Angiogram)
- Hypertension and T2D (clinical and lab tests)
- Obese, Smoker (Hx)
- Genomic profile in future and individualized treatment

Clinical syndrome
- Angina, Tiredness, SOB

Preclinical syndrome
- Atheroma
- BP
- BGlu

Proximal biomarker
- Dyslipidaemia

Distal biomarker
- GEs

Risk markers
- GEs
- GEs
- GE
- GE

Many others
- Stroke
- PVD
- Dementia
- T2D
Psychosis

Clinical syndrome

Preclinical

Proximal biomarker

Distal biomarker

Risk markers

### Multilevel Psychiatric Diagnosis of the future

- Non affective psychosis
- Dopamine dysregulation (PET?)
- Impaired cognition, defect state (Psychological testing)
- Defect of synaptic plasticity (MEG? iPSC?)
- Cannabis use (Hx and examination)
- Genomic profile and individualized treatment

### Risk markers

- GEs
- GEs
- GEs
- GEns

### Clinical syndromes

- ADHD
- ASD
- Depression
- Mania

### Many others
Main messages

- The genetics of psychiatric disorders is highly complex: risk alleles in many genes confer risk to psychiatric disorders.

- There is extensive pleiotropy: genetic risk doesn’t map onto current diagnoses.

- Current categorical diagnoses are inadequate for etiological and mechanistic research and their dominant role in the clinic is on notice.

- Genetic testing is moving into the clinic and becoming of increased relevance to psychiatrists.

- Schizophrenia is part of a spectrum of neurodevelopmental disorders including intellectual disability, autism, ADHD and bipolar disorder.

- There is promising convergence onto specific biological processes involved in synaptic function and development. These serve as a robust starting point for mechanistic studies and the development of new therapies.