Exact phenotype definition for complex genetic traits: Novel strategies to establish valid diagnostic entities in psychiatric genetics in the age of high-throughput genotyping and brain imaging

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The concept of psychopathology over time

- ## The <u>supernatural</u> model (before the 18th century)

  - psychopathology = possession by demons

  - treatment = exorcism

- ## The <u>moral</u> model (late 18th – early 19th century)

  - abnormal behavior = deliberately adopted by the individual like criminal behavior

  - treatment = confinement & other punishments

The concept of psychopathology over time

- The <u>medical</u> model (since 19th century)

    - psychopathology = product of natural causes (not necessarily biological) identifiable by techniques of empirical sciences

    - treatment is based on scientifically proven methods

Siegler & Osmond 1974

The medical model of psychopathology

Symptoms

Syndromes

Disease

...has allowed us to think

in terms of...

Course

Diagnosis

Prognosis

Etiology

...frankly, was...

...a mess!

20th century descriptive phenomenology
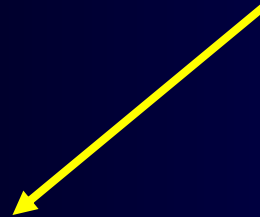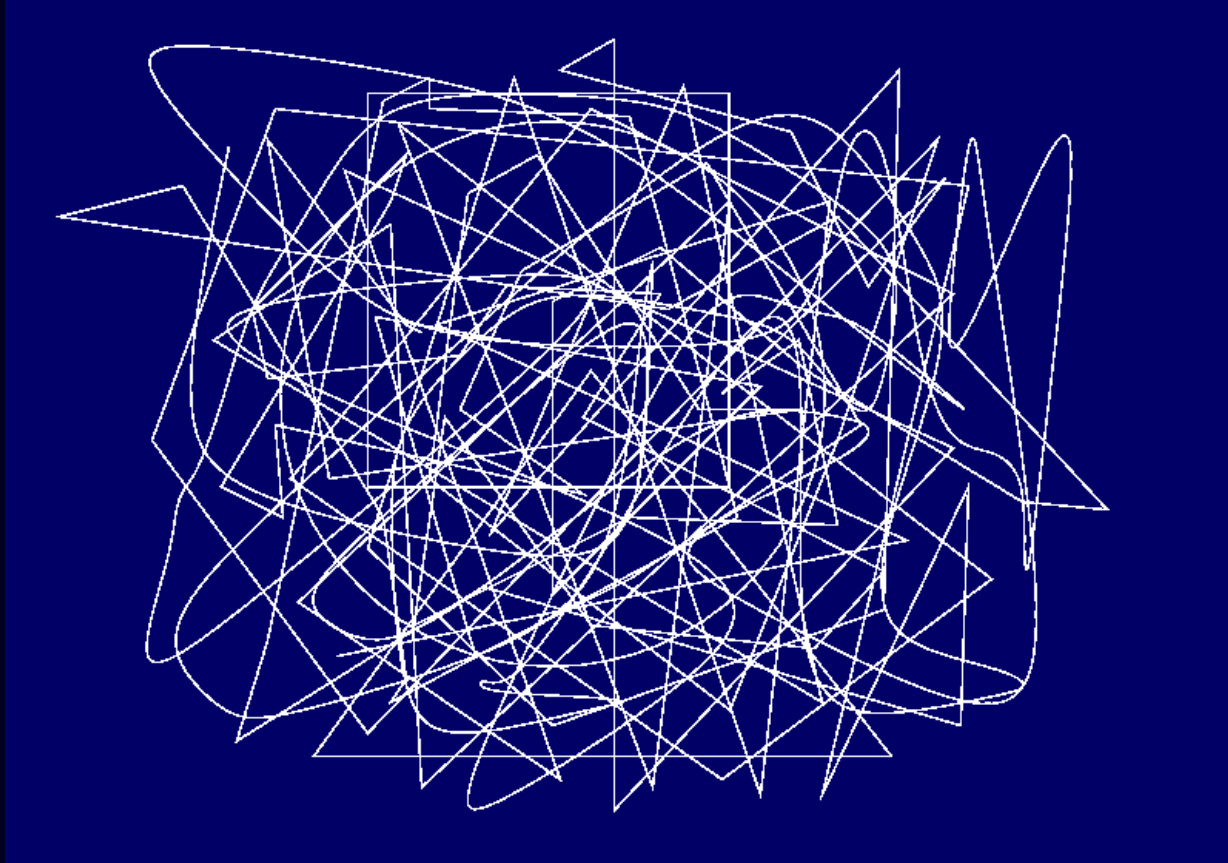
Emil Kraepelin (1856-1926)

*„I tried to bring some order into the tangle of the clinical presentations of my patients by trying **to characterize their comments and behaviour as precisely as possible**"*

- 15 categories of mental illnesses

- dichotomy between schizophrenia and manic-depressive illness (based on course of illness)

20th century descriptive phenomenology, epidemiology & genetics

- K. Leonhard (1957): separation between unipolar and bipolar mood disorder

- validated J. Angst & C. Perris (1966)

- Family, twin & adoption studies revealed familial relationships of phenoytpes

- Genetic basis of familiality

➔ Added more knowledge about psychiatric phenotypes

➔ But: No clear operational criteria

➔ Diagnoses remained unreliable

Babylonian Confusion

The neo-Kraepelinian movement (1970s) & operationalized phenotype definition

Feighner, Guze, Robins, Winokur

Spitzer, Endicott

➔ Stringent, operational diagnostic criteria (RDC, DSM-III, DSM-III-R, DSM-IV)

➔ Structured diagnostic interviews (SADS, SCID, DIGS)

➔ Basis for phenotype characterization for genetic studies

Fragebögen für psychiatrisch-genetische Untersuchungen
(Indexpatient)

- Demographische Informationen
- Anamnesebogen
- Familiäre Belastung
- Psychiatrische Vorgeschichte
- Life Events (Codierungsbogen und Dokumentationsbogen)

- SKID I: Strukturiertes Klinisches Interview für DSM-IV

- Suizidcharakteristik
- Interview zu belastenden Erlebnissen
- LHA (Life History of Aggression)
- PAS (Premorbid Adjustment Scale) – Patientenversion
- Fragebogen zum elterlichen Beziehungsverhalten
- Händigkeit
- Fragebogen zur medikamentösen Behandlung
- Fragebogen zu Medikamenten-Nebenwirkungen
- OPCRIT (Operational Criteria Checklist)

- GAS (Global Assesment Scale)

GUÍA DEL USUARIO
PARA LA
ENTREVISTA CLÍNICA
ESTRUCTURADA
PARA LO TORNOS
DEL EJ

Comprehenisve Phenotype Characterization
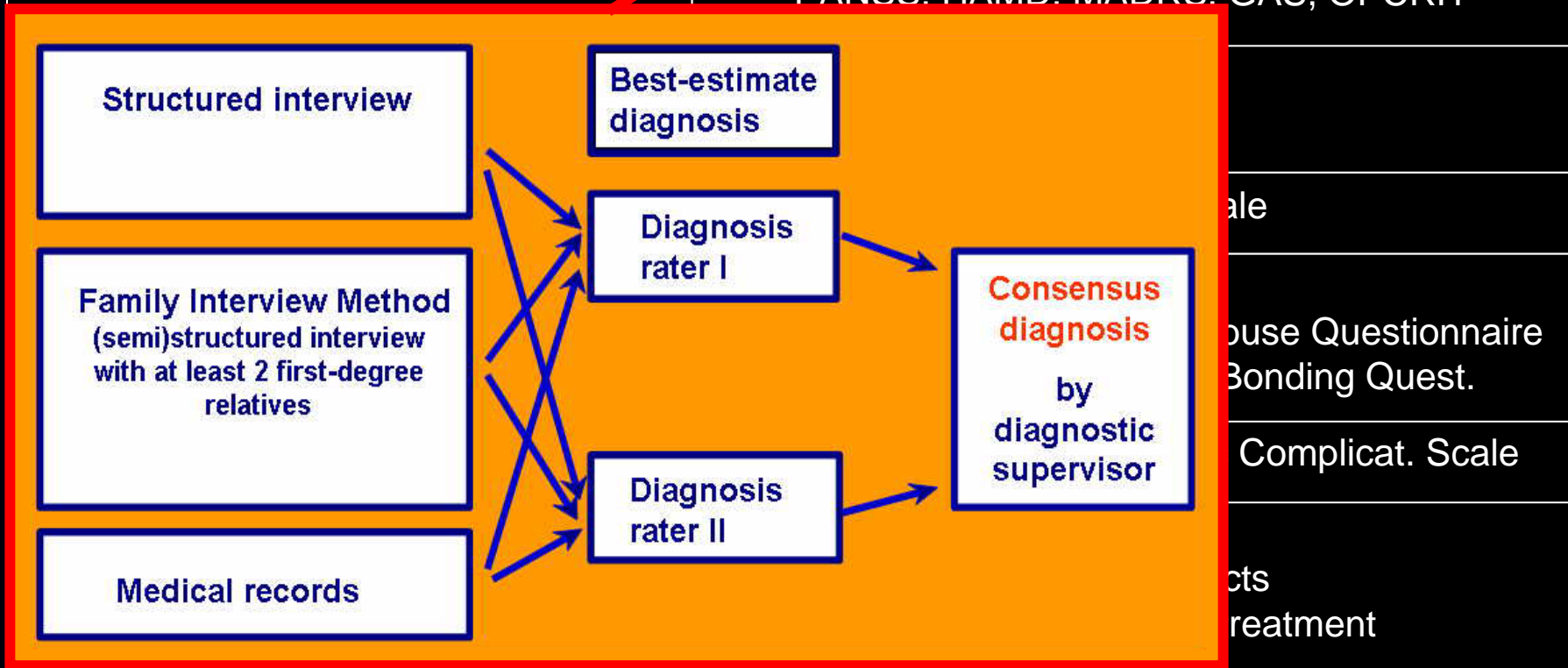
Phenotypic feature

Diagnostic instrument

Lifetime-Symptomatology & Functioning	• Semi-structured assessment of medical and psychiatric history, of demography, suicidality
	SCID I/ SCID II/ FISC
	• PANSS. HAMD. MADRS. GAS, OPCRIT

Structured interview	Best-estimate diagnosis
Family Interview Method (semi)structured interview with at least 2 first-degree relatives	Diagnosis rater I → Consensus diagnosis by diagnostic supervisor
Medical records	Diagnosis rater II →

...ale

...ouse Questionnaire
...Bonding Quest.

...Complicat. Scale

...cts
...reatment

Challenges that lie ahead

- Operationalized criteria have proven reliable and valid

- They were instrumental in linkage and association findings

BUT

- Current psychiatric diagnoses cannot yet be guided by biological data (blood test etc.)

- Operationalized criteria are constructs and subject to change (DSM-III, DSM-III-R, DSM-IV, DSM-V...)

- DSM-diagnoses still encompass heterogenous clinical pictures

Develop and use approaches that may help to define more homogenous phenotypes.

Toward greater phenotypic homogeneity

- **Macro-phenotypes**
  - Tauopathies: large group of neurodegenerative disorders (Alzheimer, Pick, supranuclear palsy) caused by mutations in the gene encoding tau
  - May capture the broad effect of some genes on pathways
  - Difficult to formulate in the absence of prior genetic findings

- **Endo-phenotypes**
  - Closer to underlying biological mechanism
  - Criteria to be fulfilled: reliability & stability, strong association with the phenotype of interest, heritability

- **Sub-phenoytpes**
  - Intuitive approach
  - Successful examples: early onset breast cancer, obese subtype of diabetes, non-syndromic deafness
  - Caveat: overstratification may lead to spurious findings

Sub-phenotyping

- Traits must be reliable to assess

- Should be stable over the cause of illness (e.g. irritability in most episodes of mania)

- Traits should be heritable, at least show familial clustering

Sub-phenotyping in bipolar affective disorder

Assessment of familiality

- Joint analyses in large samples from Germany, Andalusia/Spain, UK, Ireland, and the US

- Mixed-effects modeling of famililality of a broad range of phenotypic features

- Strong familiality observed for substance abuse, alcoholism, psychosis, history of suicide attempt, episode frequency, and level of social functioning (<u>corrected</u> p-values 0.0001-0.03)

- Candidates for covariate-based approaches

Fisfalen et al., *Am J Psychiatry*, 2005
Schulze et al., *Arch Gen Psychiatry, in press*

Sub-phenotyping in bipolar disorder

Reverse phenotyping

- „Traditional" approach:

  diagnose - genotype - analyze (forward genetics)

- Reverse phenotyping:

  genetic data used to drive new phenotype definitions

Reverse phenotyping
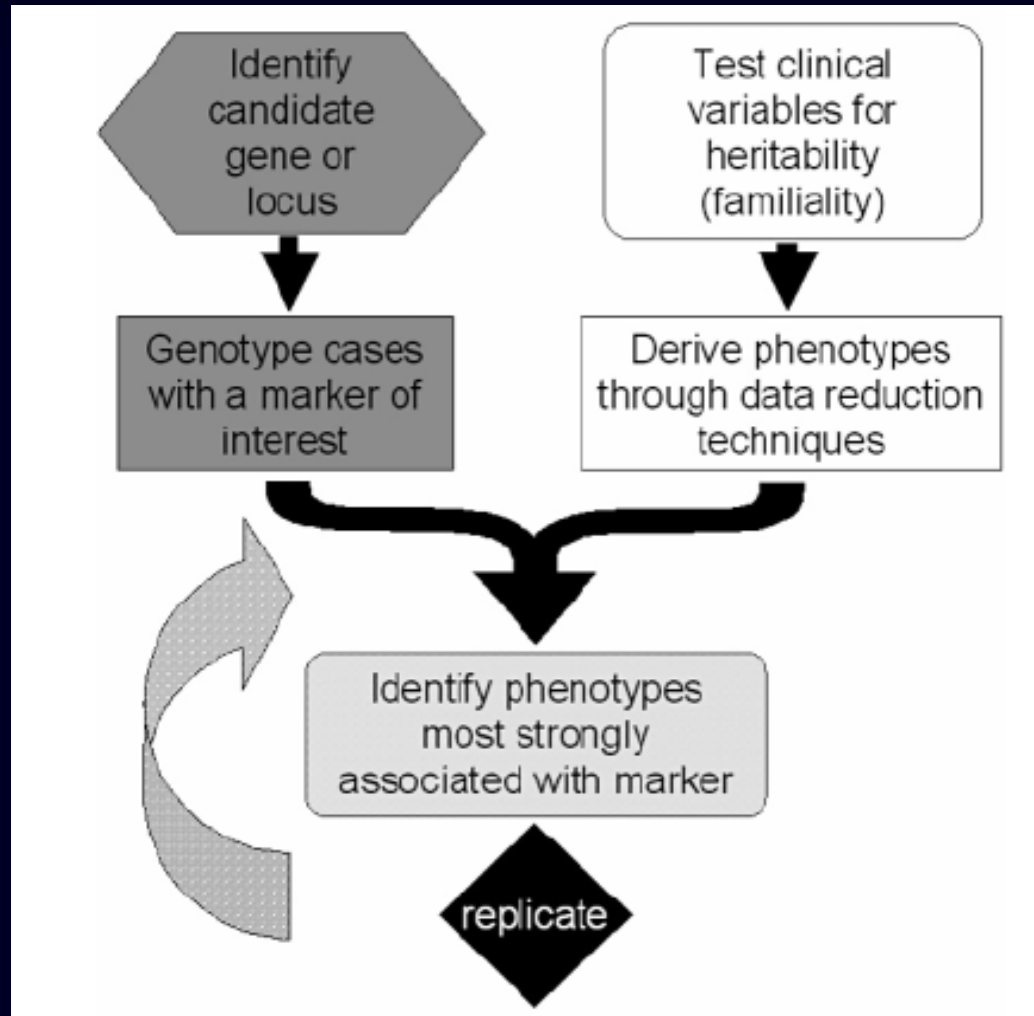
Reverse phenotyping in bipolar disorder

Article

Genotype-Phenotype Studies in Bipolar Disorder Showing Association Between the DAOA/G30 Locus and Persecutory Delusions: A First Step Toward a Molecular Genetic Classification of Psychiatric Phenotypes

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Objective: The authors previously reported an association between the D-amino acid oxidase activator (DAOA)/G30 locus and both schizophrenia and bipolar affective disorder. Given the presumed role of DAOA/G30 in the neurochemistry of psychosis and its localization in a schizophrenia and bipolar affective disorder linkage region (13q34), it was hypothesized that the bipolar affective disorder finding could be carried out by a psychotic subgroup and that a current classification on the basis of psychotic features in general might be too crude a procedure. The authors therefore tested whether confining caseness to specific psychotic features would improve detection of genotype-phenotype correlations.

Results: In a logistic regression, "persecutory delusions" were found to be the only significant explanatory variable for the DAOA/G30 risk genotype among 21 OPCRIT symptoms of psychosis. The authors therefore tested for association between DAOA/G30 and bipolar affective disorder in the 90 cases with a history of persecutory delusions. Whereas this subset showed strong association (odds ratio=1.83 for the best marker), the remaining larger sample of 165 patients with no such history did not differ from comparison subjects, suggesting that the association between DAOA/G30 and bipolar affective disorder is due to persecutory delusions. This was confirmed in an independent study of 294 bipolar affective disorder patients and 311 comparison subjects from Poland, in which an association between bipolar affective disorder and DAOA/G30 was only seen when case definition was restricted to cases with per-

Reverse phenotyping & beyond
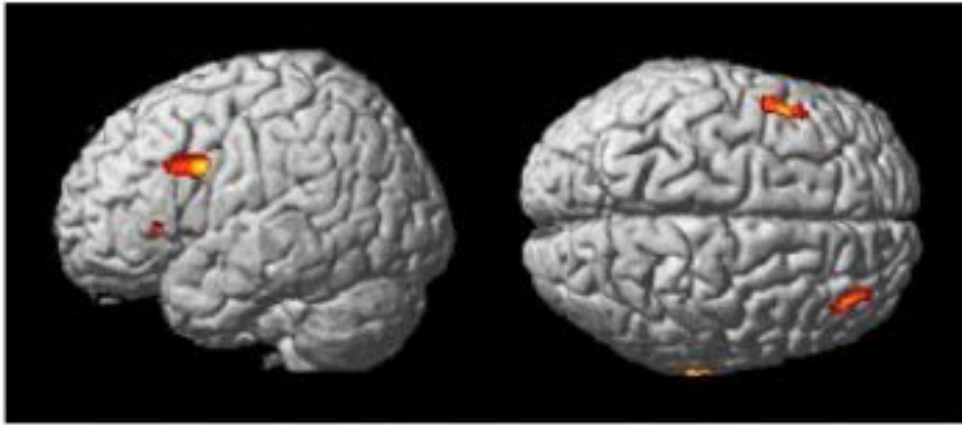
Bipolar patients showing fronto-temporal volume reduction compared to controls (structural MRI)
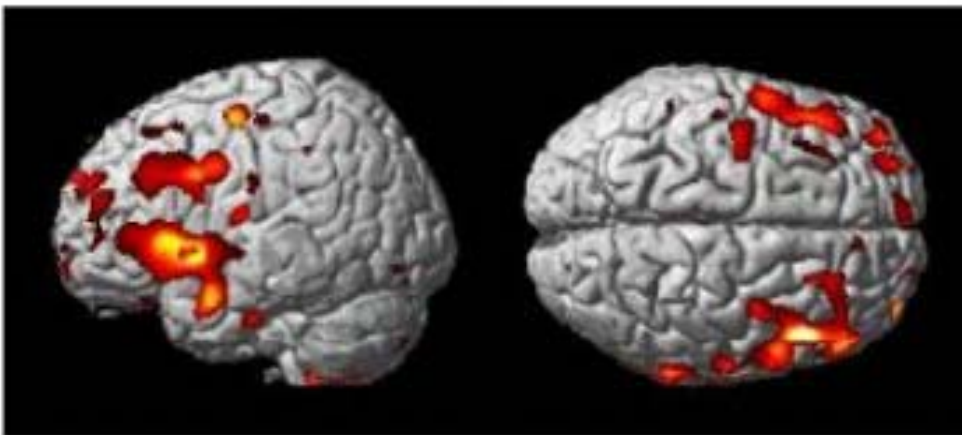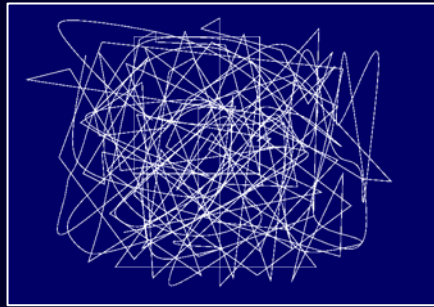
Bipolar patients with a history of persecutory delusions compared to controls

The path of psychiatric phenotyping
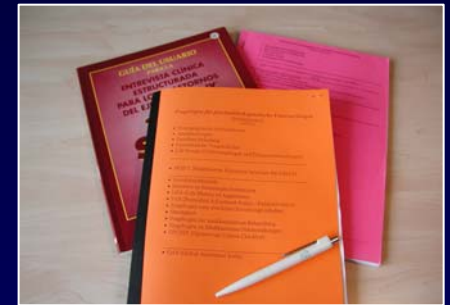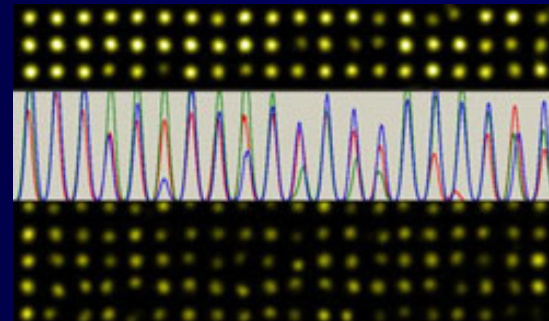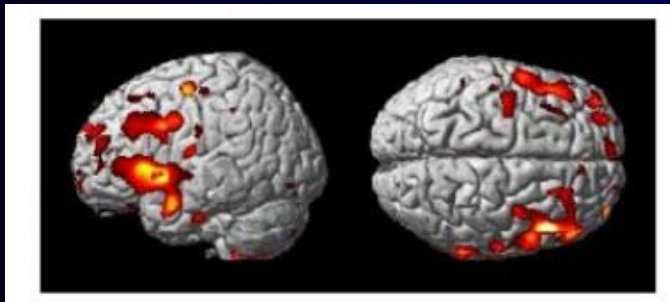

- 19th century

19th century

20th century

Last 4 decades

Future frontiers

Collaborating research groups

Division of Genetic Epidemiology (ZI): M. Deschner, A. Georgi, C. Schmäl, T.G. Schulze, H. Tost, M. Rietschel

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