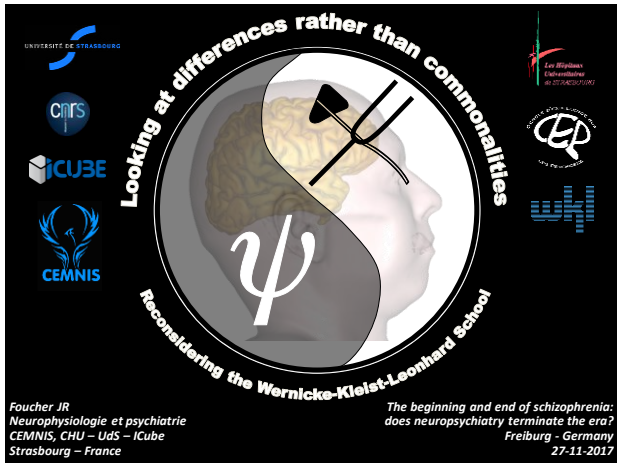
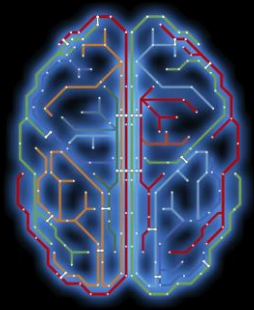


Roadmap



- Epistemological reminding: How medical sciences* are working?
- Why did psychiatry hit the wall of validity (and why neurology didn't)?
- What options for the next move in endogenous psychosis♥?
- Turning back to natural phenotypes: WKL as an illustration of a classical medical approach in (neuro)psychiatry

* Concerns the natural sciences component of medicine, not the applied sciences one (evidence based medicine)

♥ Not exogenous (secondary) not reactional

The billion Bucks' question

David J. Kupfer
(1941 -)

"Concerns have been raised that researchers' slavish adoption of DSM-IV definitions may have hindered research in the etiology of mental disorders... Reification of DSM-IV entities, to the point that they are considered to be equivalent to diseases, is more likely to obscure than to elucidate research findings.

All these limitations in the current diagnostic paradigm suggest that research exclusively focused on refining the DSM-defined syndromes may never be successful in uncovering their underlying etiologies. For that to happen, an as yet unknown paradigm shift may need to occur."

Kupfer, D.J. et al. (2002).
Introduction. In "*A Research Agenda for DSM5*"
APA, p. xviii–xix.

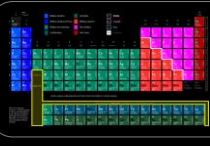
Questioning the validity of current classifications

Utility : For what purpose is it made, to what extent is it adapted?

Epidemiology, EBM

Reliability : Inter-rater agreement, test-retest reproducibility.

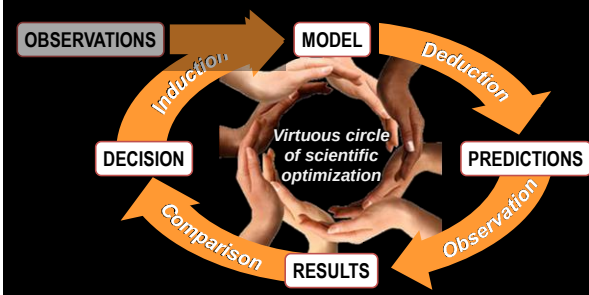
Only requirement for DSM & ICD



Validity : To what extent does it reflect the reality of the world (naturalistic / realistic paradigm).

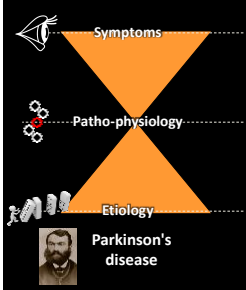
Natural sciences tends towards validity

Adapting the model to nature (reality)



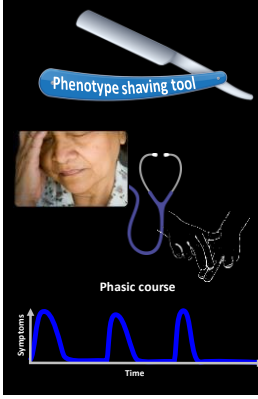
Scientific validation is an optimization process that is looking for the best match between simple and predictive causal models to reality

Scientific classification = scientific model(s)



- A scientific classification IS a model
  - Validity is how far its accounts for all observations
  - If the theory evolves, the classification evolves too ⇨ Optimization process (impossible if a-theorism: DSM / ICD)
- Medical sciences: diseases classifications are causal models
  - Diseases (naturalistic definition) : pathophysiological causal model of symptoms.
  - A disease is defined either
    - ✓ by its etiology, e.g. Huntington's D.
    - ✓ by its pathophysiology, e.g. Parkinson's D.

Scientific medicine starts with a good phenotype



- What's a good phenotype ? Parsimony principle (Occam's razor)
  1. 1 patient = 1 phenotype (long range stability)
  2. In multiplex family: 1 family = 1 phenotype
  3. 1 core disorder (elementary or fundamental) Not being blinded by coarses similarities

  ⇨ Possibly natural
- Clinical phenomenology
  - Clinical presentation(s)
    - ✓ Symptoms: complains, observation
    - ✓ Clinical signs (examination, testing)
  - Course
  - Context
    - ✓ Predisposing factors (age, heredity …)
    - ✓ Precipitating factors (toxic …)
    - ✓ Response to different treatments …

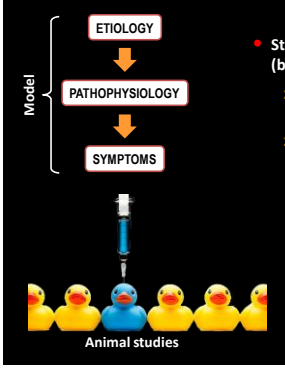
Scientific medicine starts with a correlation

- Step 1: consistent correlation (loose control of the putatively causal parameter).
  - Anatomo-clinical correlation (neurodegenerative diseases)
  - Imaging-clinical correlation (stroke, tumor …)
  - Biology-clinical correlation (metabolic disorder)
  - Immuno-clinical correlation (LED, Sneddon …)
  - Electro-clinical correlation (epilepsies)
  - Genetic-Clinical Correlation (Huntington)

⇨ "Biomarker" concept – causal relation

⇨ External validators, endophenotypes

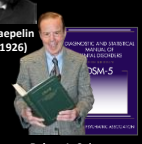
Scientific medicine ultimate validation: Controlled experiments



- Step 2 : Experimental validation (best control of the putative causal parameter)
  - Causing the dysfunction in an animal model mimic the human phenotype.
  - Correcting for the dysfunction in patients relieves the symptoms.

Why did we hit the wall of validity?

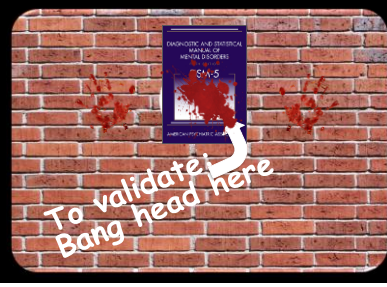
Emil Kraepelin (1856-1926)



Robert L. Spitzer (1932 - 2015)

- Normativist: pathological deviance
- Nominalist: exist in my mind as concepts
  ⇨ Consensus process
- Optimization criteria:
  - Reliability
  - 1 patient = X disorders

- Non naturalistic approach: Xdisoders, poor familial aggregation, no core symptoms / coarse "syndrome"
- Defined at the symptomatic level
- A-theoretic: nothing to optimize – remains symptomatic
- Fixed / unchangeable: non optimizable



Disorders

Beyond DSM-5 and ICD-10

Emil Kraepelin (1856-1926)

Robert L. Spitzer (1932 - 2015)

Thomas Insel (1951 -)

Bruce Cuthbert (19?? -)

Carl Wernicke (1848-1905)

Karl Kleist (1879-1960)

Karl Leonhard (1904-1988)

- Normativist: pathological deviance
- Nominalist: exist in my mind as concepts
  ⇨ Consensus process
- Optimization criteria:
  - Reliability
  - 1 patient = X disorders

Disorders

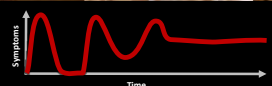
- Normativist: deviation from the norm
  ⇨ Empirical / Construct
- Optimization criteria
  - Cross-sectional:
    1 patient = X dimensions
- Purpose: drug develop.

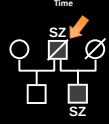
Dimensions / constructs

- Naturalist: entity existing in nature
  ⇨ Empirical process
- Optimization criteria
  - Brain system coherence
  - Longitudinal principle:
    1 patient = 1 disorder
  - Familial aggregation principle

Phenotypes

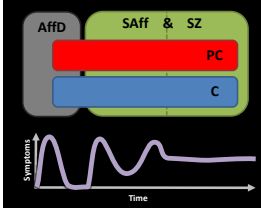
Focusing on 1 WKL phenotype: periodic catatonia



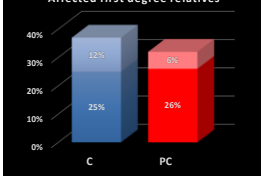


- Frequent: prevalence 0.1-0.2 % (Europe) ~ 12% of SZ & SA disorders
- ICD/DSM : psychotic and affective episodes (BPD and UD)
- Specific core symptoms: psychomotor disorganization :
  - Co-occurrence of akinesia and hyperkinesia
  - Parakinesia: distortion of expressive motility
- Relapsing-progressive course
- No ontogenic but hereditary etiology (familial aggregation):
  - Mostly with psychosis (26% 1° relative).
  - But also without psychosis (pure residual syndrome) (+ 6%).
  - Autogenic dominant with partial penetrance, ≥ 2 loci, ≥ 4 genes.

Comparing periodic catatonia (PC) to cataphasia (C)



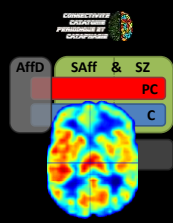
Affected first degree relatives



- Both are frequent: prevalence 0.1-0.2 % (Europe), each ~ 10-15%
- SZ, SA and affective episodes (BPD and UD)
- Relapsing-progressive course
- Specific residual syndrome (thought & language disturbances in C)
- No ontogenic component (pregnancy, birth…)
- Both familial aggregation:
  - Mostly with psychosis (saturated colors)
  - But also without psychosis (pure residual syndrome)
- BUT no crossed liability (same phenotypes within families)

Model confrontation experiment

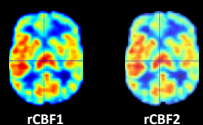
Single diathesis model



WKL multiple diathesis model

- SZ - SA model predictions
  - Only common differences
    PC vs CTR = C vs CTR
  - No specific differences between PC and C
    i.e. C vs CTR = C vs. PC
    & PC vs CTR = PC vs. C
- Correlation with a biomarker : rCBF (Step 1)
  - Specific rCBF changes ?
  - With structure-function correspondence ?
- PC & C models predictions
  - Limited and irrelevant common differences
    PC vs CTR = C vs CTR
  - Specific & relevant differences, i.e. double dissociation
    PC vs CTR = PC vs. C
    & C vs CTR = C vs. PC

Methods



Common (conjunction)
CTR vs. PC & CTR vs. C

Specific (conjunction)
C vs. CTR & C vs. PC
PC vs. CTR & PC vs. C

Conjunction
rCBF1 & rCBF2

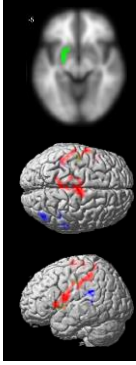
&

Results

- Paired controls (n = 28)
- Patients: double diagnosis of SZ / Sz-Aff & WKL phenotypes :
  - C: Cataphasia (n = 9)
  - PC: Periodic Catatonia (n = 20)
  - CTR (n = 36)
- MRI
  - Anatomical 3D-T1 (MP-RAGE) and FLAIR (exclusion of brain anomalies)
  - ASL (QUIPS II)
    - ✓ TE = 9.7 (pure ASL) – Passively looking at movie
    - ✓ TE = 21 ms (ASL-BOLD) – Active tasks
- Analysis
  - rCBF conversion, distortion correction, normalization, smoothing
  - Same SPM analysis on the two ASL
  - Only looking at common results (no artifact or task effect). $p_{unc} < 6.25 \cdot 10^{-6}$, $k > 1$ cm³

Results & interpretations

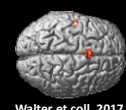
PC C SZ



SZ vs. CTR : ⇗ rCBF L striatum & premotor Cx
Classical antipsychotics effect
No hypo DLPFCx ⇨ Cycloid psychoses

Double dissociation :

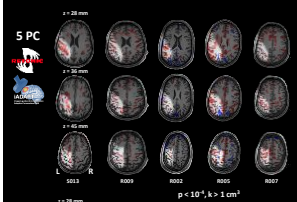
- Periodic catatonia
  Specific ⇗ rCBF L motor & premotor Cx
  Structure function correspondence
  MODEL : Inhibition deficit in SM/PMCx?
  ⇨ TTT: BdZ, CLZ > AP, ECT



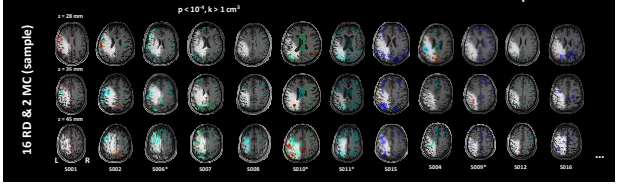
Walter et coll. 2017
20 SZ + ≥ 1 Σ BFCRS
vs. SZ Ø Σ BFCRS

- Cataphasia
  Specific ⇘ rCBF TPJ bilaterally
  Correlation with TePEO-C (r = - 0.68, p = 0.012)

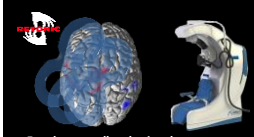
Step 1: consistency
Left SM & premotor hyperactivity as a biomarker



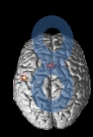
- Method
  - Single subject analysis
  - 3 MRI with 2 ASL / rCBF measurements
  - Conjunction analysis SnPM + SPM vs 40 CTR
- Results
  - 5 PC patients
  - Never observed in 2 mannered catatonia & 16 resistant depressions



Step 2: controlled experiment
Correcting left SM & premotor Cx hyper-activity

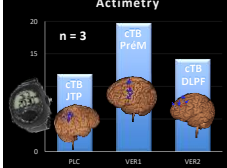


Foucher et coll. submitted



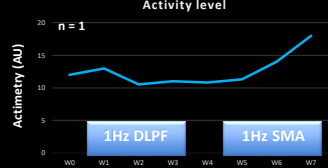
Walter et coll. 2017

Actimetry



Foucher et coll. unpublished

Activity level

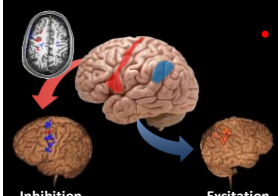


Walter et coll. unpublished

Conclusions

The WKL school

- Classical scientific medicine
  - Putatively natural phenotypes (core symptoms, life-long, familiarly consistent)
  - Step 1: Looking for a correlated pathological dysfunction, if consistent ⇨ biomarker
    if putatively causal ⇨ model
  - Step 2: Alleviating symptoms by correcting the pathological dysfunction ⇨ Treatment
- WKL school embraced this naturalist approach (natural sciences)
  ≠ DSM (± ICD) & ≠ RDoCs, both are normativist approaches (applied sciences)
- There might well be diseases in the endogenous psychosis spectrum
  - Periodic catatonia could be the first !
  - (Cataphasia the second?)



Inhibition Excitation

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Thank you for your attention