TOWARDS A CLINICAL METHODOLOGY FOR NEUROPSYCHOPHARMACOLOGICAL RESEARCH

Development of Neuropsychopharmacology
1950s

PHARMACOTHERAPY (1952 - 1957)

PSYCHOPHARMACOLOGY

NEUROTRANSMITTERS (1952-1960)

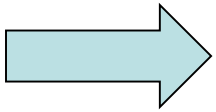
SPECTROPHOTOFLUORIMETER (1955)

NEUROPHARMACOLOGY

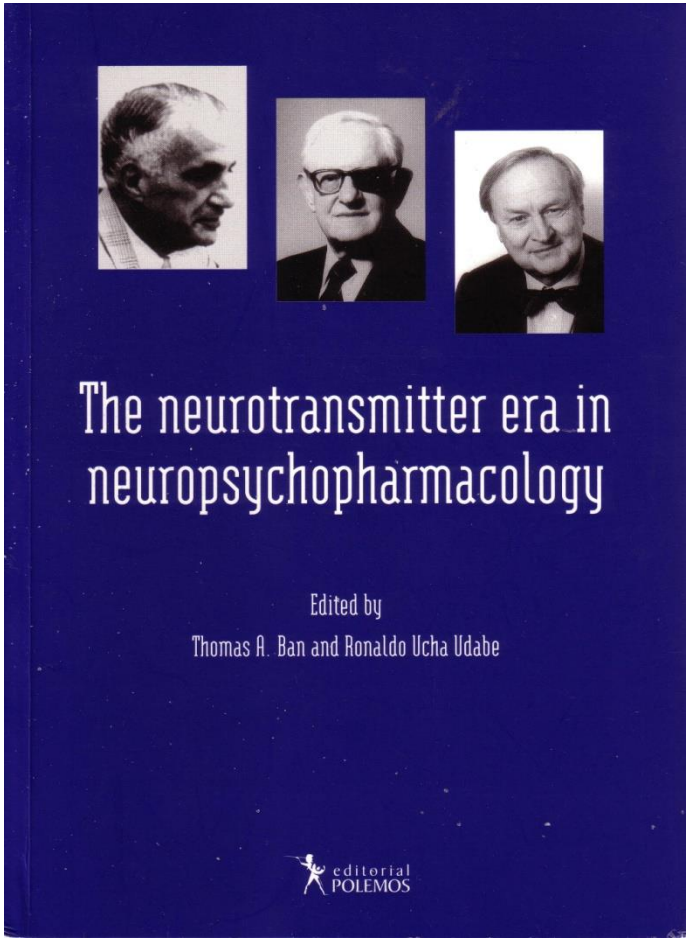
NEUROPSYCHOPHARMACOLOGY (1957)
Birth of composite discipline

NEUROPSYCHOPHARMACOLOGY
LINKS THE EFFECT OF A DRUG ON MENTAL ILLNESS
WITH ITS EFFECT ON BRAIN STRUCTURES
INVOLVED IN ITS MODE OF ACTION

KNOWLEDGE

PATHOPHYSIOLOGY OF ILLNESS  **MORE SELECTIVE DRUG**

NEUROTRANSMITTER ERA
First Epoch In the History of Neuropsychopharmacology



NEUROTRANSMITTER ERA
NEUROPHARMACOLOGY

Spectrophotofluorimeter & Receptor Binding Assays

Neurotransmitter dynamics
metabolism
regional distribution
effect of drugs on uptake & release

Affinity of drugs to neurotransmitter receptors

NEUROTRANSMITTER ERA PSYCHOPHARMACOLOGY

Rating Scales & Consensus Based Diagnoses

Statistical Methodology (RCT)

- **efficacy**
- **efficacy in more than one diagnosis**

BY LINKING THE MODE OF ACTION OF A DRUG WITH A PHARMACOLOGICALLY HETEROGENEOUS POPULATION, NEUROPSYCHOPHARMACOLOGICAL RESEARCH PROVIDED RELEVANT FEEDBACK ONLY TO THE DEVELOPMENT OF DRUGS WITH DIFFERENT ADVERSE EFFECTS

FROM THE NEUROTRANSMITTER TO THE GENETIC ERA

GAP BETWEEN NEUROPHARMACOLOGY WITH CAPABILITY TO TAILOR DRUGS TO RECEPTOR AFFINITIES BY GENETIC TECHNOLOGY AND PSYCHOPHARMACOLOGY WITH METHODOLOGY RESTRICTED TO DEMONSTRATION OF THERAPEUTIC EFFICACY

INCONSISTENT AND CONFLICTING FINDINGS IN MOLECULAR GENETIC RESEARCH

FROM THE NEUROTRANSMITTER TO THE GENETIC ERA

RECOGNITION THAT:

PRIMARY TARGETS OF PSYCHOTROPIC DRUGS ARE ENCODED BY GENES THAT HAD BEEN IDENTIFIED

ANY CLINICAL ENTITY THAT CORRESPONDS WITH A TREATMENT RESPONSIVE POPULATION IS SUITABLE FOR THE GENERATION OF GENETIC HYPOTHESES OF MENTAL ILLNESS

PROGRESS IN MOLECULAR GENETIC RESEARCH DEPENDS ON IDENTIFYING PHARMACOLOGICALLY HOMOGENEOUS POPULATIONS

ALTERNATIVE APPROACHES

BREAK-UP INTO SIMPLE BIOLOGICAL COMPONENTS

RE-CONCEPTUALIZE IN DISCRETE BIOLOGICAL DEFICITS

Alternative Phenotypes for Schizophrenia

Abnormality of smooth pursuit eye movement; short arm of chromosome 5

P-50 evoked response deficit; α_1-nicotinic acid receptor on long arm of chromosome 15

GENETIC PSYCHIATRIC NOSOLOGY

TOWARDS THE COMPOSITE DIAGNOSTIC EVALUATION (CODE) SYSTEM

RECOGNITION THAT:

THERE IS NO ALTERNATIVE METHODOLOGY TO PSYCHIATRIC NOSOLOGY FOR CLASSIFYING MENTAL PATHOLOGY IN A CLINICALLY RELEVANT MANNER

IDENTIFICATION OF TREATMENT RESPONSIVE FORMS OF ILLNESS IS PREREQUISITE FOR PROGRESS

DIFFERENTIAL RESPONSIVENESS TO A PSYCHOTROPIC DRUG WITHIN A DIAGNOSTIC CATEGORY CANNOT BE EXPLAINED BY PHARMACOKINETIC DIFFERENCES

TOWARDS THE CODE SYSTEM

INCONSISTENT FINDINGS WITH LINEAR REGRESSION EQUATIONS IN WHICH RATING SCALE SCORES WERE USED

FRANK FISH'S (1964) FINDINGS THAT 86% OF PATIENTS WITH AFFECT-LADEN PARAPHRENIA & LESS THAN 25% OF PATIENTS WITH SYSTEMATIC SCHIZOPHRENIA RESPONDED TO NEUROLEPTIC PHENOTHIAZINES

DEMONSTRATION THAT CONSENSUS-BASED DIAGNOSES (DSM-IV) COVER-UP THEIR COMPONENT DIAGNOSES

Vital Depression
Affect-laden Schizophrenia

THE CODE SYSTEM

METHODOLOGY FOR THE IDENTIFICATION OF TREATMENT RESPONSIVE FORM OF ILLNESS BY UNCOVERING DIAGNOSES

VOCABULARY	PSYCHOPATHOLOGIC SYMPTOM PROFILE
STRUCTURED INTERVIEW	
DIAGNOSTIC ALGORITHMS	DIAGNOSTIC PROFILE
RATING SCALE FOR SEVERITY	SEVERITY SCORE

READILY ACCESSBILE INFORMATION RELEVANT TO THE DIAGNOSTIC PROCESS FROM THE LOWEST TO THE HIGHEST LEVEL OF DECISION MAKING

CODE-AD, DD, HD, SD

PETER GASZNER

THOMAS A. BAN

CODE-HD

Composite Diagnostic Evaluation of Hyperthymic Disorders

BUDAPEST
1998

CODE-DD
1896-1987

VOCABULARY	**90 items (codes)**
STRUCTURED INTERVIEW	
DIAGNOSTIC ALGORITHMS	**25 classifications**
RATING SCALE FOR SEVERITY	**40 items (codes)**

VALIDITY	**1st Study**	**239 pts**	**99.6%**
	2nd Study	**322 pts**	**97.2%**
RELIABILITY	**1st Study**		**87.2%**
	2nd Study		**100.0%**

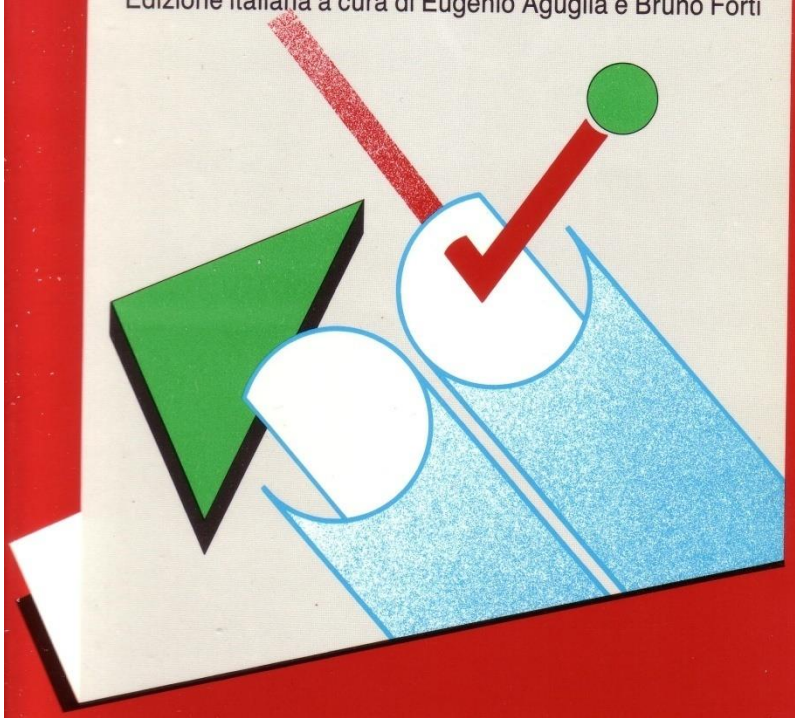
Translations & adaptations from the English original: Estonian, French, Hungarian, Italian, Polish and Portuguese

THOMAS A. BAN

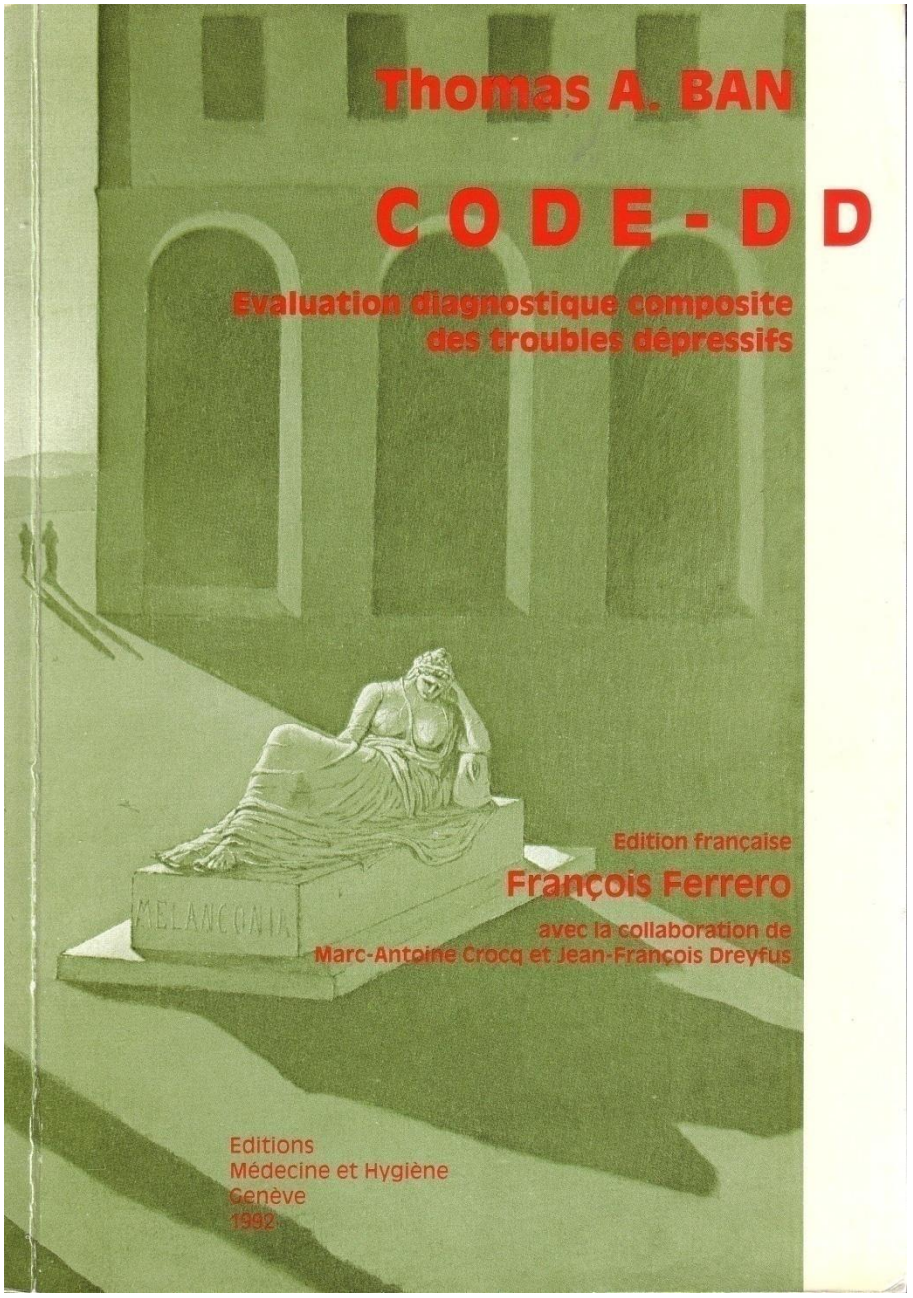
CODE-DD

VALUTAZIONE E DIAGNOSI DEI DISTURBI DEPRESSIVI

Edizione italiana a cura di Eugenio Aguglia e Bruno Forti



Liviana
Editrice



Thomas A. BAN

CODE-DD

Evaluation diagnostique composite des troubles dépressifs

Edition française

François Ferrero

avec la collaboration de
Marc-Antoine Crocq et Jean-François Dreyfus

Editions
Médecine et Hygiène
Genève
1992

CODE-DD
HYPOTHESES

MAJOR DEPRESSION IS A BROAD DIAGNOSTIC CATEGORY
If depression would be characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes, from the 322 patients with theDSM-III-R clinical diagnosis of major depression only 119, i.e., 37%would have qualified for depression

MAJOR DEPRESSION IS MORE THAN ONE FORM OF ILLNESS
From the 322 patients only 95 (29.5%) fulfilled definite criteria of Kraepelin's depressive states and 45 (14%) Schneider's vital depression with little overlap between the two forms of illness

CODE-UD

Hippocrates (460-377BC) TO DSM-IVTM (1994)

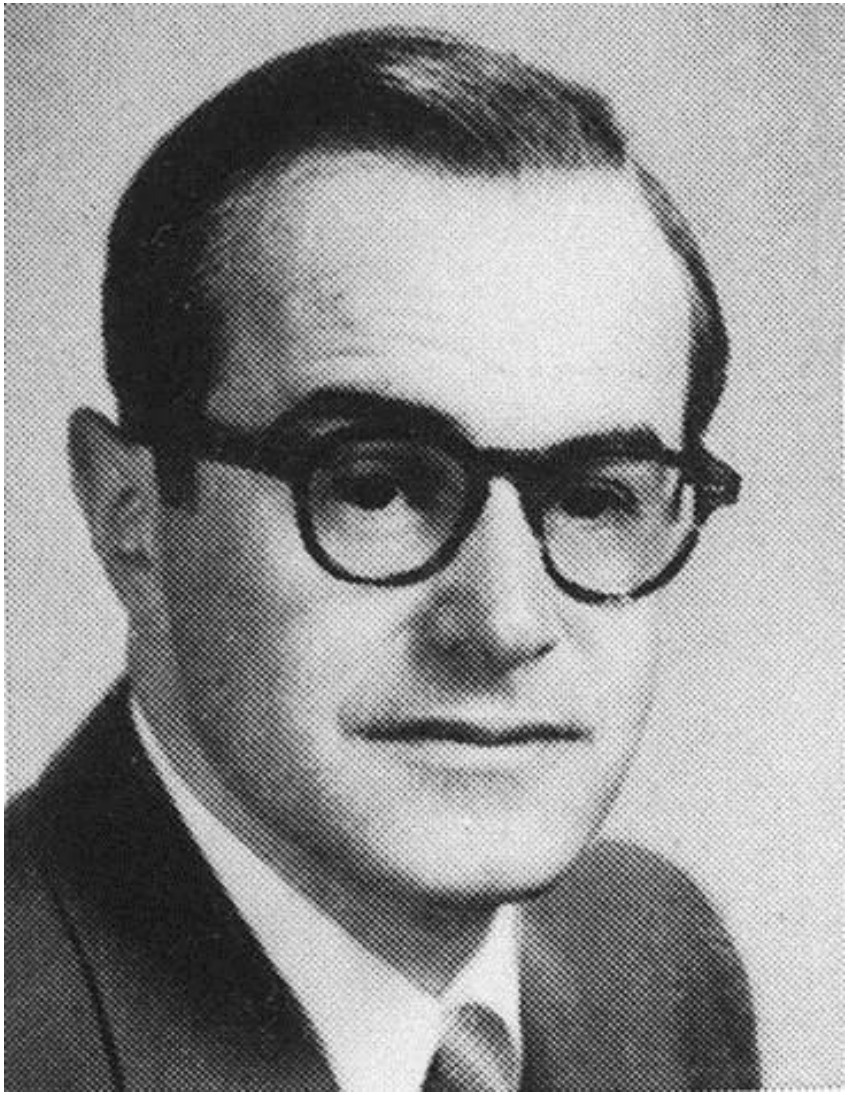
Maximizes potential of uncovering diagnoses

MELANCHOLIA

Hippocrates	**5th BC**	**Chronic Mental Disease**
Sauvages	**1769**	**Insanity With Disturbed Cognition**
Cullen	**1769**	**Insanity With Disorder of Judgment**
Heinroth	**1818**	**Insanity With Depression of Emotions**
Esquirol	**1838**	**Lypemania (Melancholia) vs.Monomania**

CODE SYSTEM
Methodology for the identification of treatment responsive form of illness if covered up by consensus-based diagnoses

NOSOLOGIC MATRIX
Methodology for the development of empirically derived pharmacologically valid classification



Fritz Freyhan
First proposed pharmacological re-evaluation of Kraepelinian nosology with the employment of target symptoms

NOSOLOGIC HOMOTYPING
by
NOSOLOGIC MATRIX
on the basis of
PSYCHOPATHOLOGIC SYMPTOMS &
PSYCHIATRIC NOSOLOGY

IT WAS IN 2002 FIRST THAT
NOSOLOGIC HOMOTYPING
A METHODOLOGY FOR PHARMACOLOGICAL RE-EVALUATION
OF PSYCHIATRIC NOSOLOGY WAS PROPOSED

NOSOLOGIC HOMOTYPES
ARE IDENTICAL IN ELEMENTARY UNITS
(PSYCHOPATHOLOGICAL SYMPTOMS)
AND ARE
assigned the same position in the nosologic matrix constructed with the employment of three nosologic organizing principles:
TOTALITY
TEMPORAL ORGANIZATION
SPATIAL ORGANIZATION

NOSOLOGIC MATRIX
Elementary Units

The elementary units of mental illness in the nosologic matrix are psychopathologic symptoms (1920s)

Psychopathologic symptoms are accessible to pharmacologic manipulation to psychotropic drugs (1950s)

Psychotropic drugs are substances with an effect on the transmission of impulses at the synaptic cleft (1950s)

Psychopathologic symptoms are manifestations in the processing of mental events with each symptom representing a distinct pathology (2002)

Each psychopathologic symptom profile is a potential phenotype of a mental disorder

NOSOLOGIC MATRIX
Elementary Units

The psychopathologic symptom profile is derived by the determination of the “presence” or “absence”of psychopathologic symptoms included in a comprehensive list of psychopathologic symptoms

PSYCHOPATHOLOGIC SYMPTOM SCALES

Afferent (perceptual-cognitive) Scale 1
Central (relational-affective) Scale 2
Efferent (adaptive-psychomotor)Scale 3

Some of the symptoms of Scale 1

accelerated thinking
agrammatism
akoasma(s)
alogia
anesthesia
asyndetic thinking
auditory hallucination(s)
autistic delusion(s)
autoscopic hallucination(s)
bizarre delusion(s)
circumstantial thinking
coenesthetic hallucination(s)
command hallucination(s)

Nosologic Matrix
FIRST ORGANIZING PRINCIPLE

TOTALITY (Esquirol 1838)
Mania vs Monomania

Esquirol 1838 **Total vs. Partial**
Partial insanity: Personality remains preserved

Westphal 1878 **True vs. Abortive**
Abortive insanity: Insight that thinking/feelings/actions are pathological

Wernicke1899 **Universal vs. Selective**
Selective insanity: Disorientation is restricted to allo- or auto-or somatopsychic

Leonhard 1957 **Complete vs. Incomplete**
Incomplete : Restricted to one or two components of the psychic reflex

Nosologic Matrix
SECOND ORGANIZING PRINCIPLE

TEMPORAL ORGANIZATION (Kraepelin 1899)
Dementia Praecox vs. Manic-depressive Inanity

Attacks	**episodes last from minutes to hours**
Phases	**episodes last from days to years**
Periods	**phases recur with regularity**
Thrusts	**acute events yield lasting changes**
Continuous process	**chronic events yield differentiated end-states**
Progressive deterioration	**chronic events yield de-differentiation**

Nosologic Matrix
THIRD ORGANIZING PRINCIPLE

SPATIAL ORGANIZATION-POLARITY (Leonhard 1957)
Manic-depressive disease vs. Pure mania/melancholia

Bipolar (polymorph/multiform)
swings between two poles of mood/emotions/motility;
displays continuously changing variable picture

Unipolar (monomorph/pure)
restricted to one pole of mood/emotions/motility;
displays same picture within & across episodes

NOSOLOGIC HOMOTYPES

NOSOLOGIC HOMOTYPES BASED ON THE NOSOLOGIC MATRIX ARE MORE HOMOGENEOUS POPULATIONS THAN ANY OF THE DIAGNOSTIC POPULATIONS IDENTIFIED BY THE AVAILABLE DIAGNOSTIC INSTRUMENTS

THE INFORMATION GENERATED BY THE USE OF THE NOSOLOGIC MATRIX WOULD ALLOW THE COMPLETION OF THE RE-EVALUATION OF KRAEPELINIAN DIAGNOSTIC CONCEPTS STARTED BY PSYCHIATRISTS AT THE HEIDELBERG CLINIC IN THE 1920s

NOSOLOGIC HOMOTYPES

IF THE INFORMATION COLLECTED BY THE NOSOLOGIC MATRIX WOULD NOT IDENTIFY PHARMACOLOGICALLY OR GENETICALLY HOMOGENOUS POPULATIONS IT WOULD INDICATE THAT PSYCHOPATHOLOGY AND PSYCHIATRIC NOSOLOGY HAVE NOTHING TO OFFER TO BIOLOGICAL PSYCHIATRIC RESEARCH AND GENERAL PSYCHOPATHOLOGY SHOULD BE REPLACED BY A FUNCTIONAL PSYHOPATHOLOGY AND THE NOSOLOGICAL DISEASE MODEL BY A REACTION-FORM BASED DISEASE MODEL AS SUGGESTED BY VAN PRAAG (1992, 2000)

NOSOLOGIC HOMOTYPES

IF THE INFORMATION COLLECTED BY THE NOSOLOGIC MATRIX IDENTIFIES PHARMACOLOGICALLY OR GENETICALLY HOMOGENOUS POPULATIONS IT WOULD INDICATE THAT NOSOLOGICAL HOMOTYPING COULD PROVIDE THE KEY FOR THE DELINEATION OF BIOLOGICALLY MEANINGFUL DISEASE CATEGORIES AND BY LINKING THE MODE OF ACTION OF PSYCHOTROPIC DRUGS TO PHARMACOLOGICALLY HOMOGENEOUS POPULATIONS IT WOULD BREAK THE IMPASSE IN THE PROGRESS OF NEUROPSYCHOPHARMACOLOGICAL RESEARCH, PHARMACOTHERAPY, AND MOLECULAR GENETIC RESEARCH IN MENTAL ILLNESS

NOSOLOGIC HOMOTYPES

CONSIDERING THAT NOSOLOGICAL HOMOTYPES ARE DEFINED IN TERMS OF THEIR EFFECT ON PROCESSING OF MENTAL EVENTS, AND PSYCHOTROPIC DRUGS ARE DEFINED IN TERMS OF THEIR EFFECTS ON SIGNAL TRANSADUCTION IN THE BRAIN, THE EMPIRICALLY DERIVED DIAGNOSTIC CATEGORIES COULD PROVIDE CLINICAL ENTITIES WHICH ARE SUITABLE FOR TESTING HYPOTHESES RELEVANT TO THE RELATIONSHIP BETWEEN PROCESSING OF MENTAL EVENTS AND SIGNAL TRANSDUCTION IN THE CENTRAL NERVOUS SYSTEM

NOSOLOGIC HOMOTYPES

NOSOLOGIC HOMOTYPING COULD OPEN A NEW PERSPECTIVE FOR THE DEVELOPMENT OF A PSYCHIATRY IN WHICH MENTAL PATHOLOGY IS PERCEIVED IN TERMS OF PATHOLOGY IN SIGNAL TRANSDUCTION IN THE BRAIN AND FOR THE DEVELOPMENT OF A RATIONAL PHARMACOTHERAPY OF MENTAL ILLNESS