Jürgen Zielasek

Concepts of mental disorders
Why do we use the term „mental disorder“ and not „mental illness“?

Current classification systems make no assumptions about causative factors or nosological entities

„anosological approach“
Distinct pathophysiological processes

initiate

Preformed patterns of reactions under given circumstances

lead to

Symptoms and Syndromes

Nach P. Hoff: Nosologische Grundpostulate bei Kraepelin
Early proposal of an a-nosological diagnostic approach

Die 'Erscheinungsformen des Irreseins' sind die 'natürliche Antwort der menschlichen Maschine', die 'auf das Spiel vorgebildeter Einrichtungen unseres Organismus' durch Beeinträchtigung 'gleicher Gebiete' zurückgehen.

E. Kraepelin (1920)

The 'patterns of mental disorders' are the 'natural response of the human machinery', which trace back to the 'interplay of preformed mechanisms of our organism' due to the disturbance of 'identical areas'.
New concepts in psychopathology: Aiming at nosological entities? An a-nosological concept of mental disorders (Kraepelin 1920)

Jackson’s concept of hierarchical layers of the nervous system

Causes
exogenous/endogenous

destroy, trigger, excitate, inhibit

Preformed Mechanisms

Overarching Structures

Basic Dysfunctions
Pathogenesis

Phenotypes*
(Patterns of Mental Disorders)

Forms of Expression
Pathoplastics
(sensu Birnbaum 1919)

Personality

Developmental concepts of phylogensis and ontogenesis

*L Analogous to Bonhoeffer's Reaction Types
How are mental disorders classified and diagnosed?

• International Classification of disorders (WHO) 10th Revision (ICD-10) (1992)

• Diagnostic and Statistical Manual, 5th Revision (DSM-5) (2013)
Groups of Disorders in ICD-10

F0  Organic including symptomatic disorders
F1  Substance-related disorders
F2  Schizophrenia, schizotypal and delusional disorders
F3  Affective disorder
F4  Neurotic, stress-related and somatoform disorders
F5  Eating disorders
F6  Personality disorders
F7  Intelligence disorders
F8  Developmental disorders
F9  Mental disorders of childhood and adolescence
F99 Other mental disorders
Predictive value of operationalised mental disorders

Example: „Schizophrenia“ (stability of dx over 3 years)

<table>
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<tr>
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<th>ICD-10 F20</th>
<th>DSM-III-TR 295.x</th>
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n=168 Patients

Amin et al., Br J Psychiatry 1999; 175: 537-543
Characteristics of modern psychiatric classification systems

- Globally standardised with high **reliability**
- Highly **operationalized** with standardized diagnostic procedures
- Detecting such disorders has **therapeutic** and **prognostic** relevance
- Systems are **atheoretical**
- Systems are **anosological** (in that they make no pathophysiological assumptions)
- Disadvantage:
  - Etiopathogenetically different syndromes may be combined in a single diagnostic group

→ Question of Validity
Diagnostic validity in psychiatric illness

- Clinical description
- Laboratory studies
- Delimitation from other disorders
- Follow-up studies
- Family studies

Robins and Guze (1970)
„Diese Symptome heiße ich Schizophrenie“

Symptome ersten Ranges (Erstrangsymptome):
Dialogische Stimmen, kommentierende Stimmen, Gedankenlautwerden
Leibliche Beeinflussungserlebnisse
Gedankeneingebung, Gedankenentzug. Gedankenausbreitung,
Willensbeeinflussung
Wahnwahrnehmung

Symptome zweiten Ranges
Sonstige akustische Halluzinationen
Zönästhesien im engeren Sinne
Optische Halluzinationen, Geruchshalluzinationen,
Geschmackshalluzinationen
Einfache Eigenbeziehung, Wahneinfall

Kurt Schneider „Klinische Psychopathologie“, 8. erg. Auflage, 1967

→ Dennoch ist der Gedanke nicht aufgegeben worden, dass dahinter
eigene Krankheitseentitäten stehen
Diagnostic Criteria of Schizophrenia in DSM-5

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. Social/occupational dysfunction

C. Duration (6 months)

D. Schizoaffective and Mood Disorder Exclusion

E. Substance/General Medical Condition Exclusion

F. Relationship to a Pervasive Developmental Disorder

Functional impairment is included as a mandatory criterion of schizophrenia in DSM-5.

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Psychopathological Dimensions of Psychosis

- Analysis of 39 studies
- Numbers of factors (dimensions) varied between 2-11
- The majority of studies reported $4(-5)$ dimensions:
  - Positive symptoms
  - Negative symptoms
  - Disorganization
  - Affective symptoms (some studies differentiated depressive vs. manic resulting in a five-factor solution)

<table>
<thead>
<tr>
<th>Hallucinations</th>
<th>Delusions</th>
<th>Disorganized Speech</th>
<th>Abnormal Psychomotor Behavior</th>
<th>Negative Symptoms</th>
<th>Impaired Cognition</th>
<th>Depression</th>
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**Scoring and Interpretation**

Each dimension is rated on a 5-point scale:

0 = none;  
1 = equivocal;  
2 = present, but mild;  
3 = present and moderate;  
4 = present and severe

Each rating level has a symptom-specific definition.

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A mental disorder is a syndrome characterized by *clinically significant disturbance* in an individual’s cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities. (...)

**Criterion for Clinical Significance:** “...in the absence of clear biological markers or clinically useful measurements of severity for many mental disorders, it has not been possible to completely separate normal and pathological symptom expressions contained in diagnostic criteria. (...) Therefore, a generic diagnostic criterion requiring distress or disability has been used to establish disorder thresholds, usually worded `the disturbance *causes clinically significant distress or impairment* in social, occupational, or other important areas of functioning’”.

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Wakefield’s Concept of „Harmful Dysfunction“

Harmful Dysfunction

„Value“-term
judged negative by sociocultural standards

„Scientific factual“ term
refers to the failure of an internal mechanism to perform one of its naturally selected functions

Concepts of mental disorders

**DSM-5:**
Functional impairments as an essential diagnostic element

**ICD-11:**
Functional impairments only considered if absolutely unavoidable
‘Psychiatric comorbidity’: an artefact of current diagnostic systems?†

MARIO MAJ

Four reasons for increasing rates of „comorbidity“

1. Unspoken rule that symptoms should not be present in different mental disorders
2. Increasing numbers of diagnostic groups
3. Limited number of hierarchical steps
4. Operationalizing classification criteria may lead to a loss of the „Gestalt“ aspect of mental disorders

Maj M, Br J Psychiatry 2005; 186: 182-184
New empirical approaches towards comorbidity

Figure 2. The DSM-IV symptom space. Symptoms are represented as nodes and connected by an edge whenever they figure in the same disorder. Color of nodes represents the DSM-IV chapter in which they occur most often.
doi:10.1371/journal.pone.0027407.g002

Mental disorders – only a convention or correlate of a real disorder?

Mental disorder

Only a convention used by the authors of classification systems („nomological concept“) „anosological concept“ (Kraepelin 1920)

Disorders existing in the real world („nosological entities“) Re. Griesinger

Is there a real world correlate of any mental disorder?
• Approximately 850 risk loci
• Considerable overlap with other disorders
• None of the associations suitable for individual diagnostics or classification

Harrison & Weinberger, Mol Psychiatry 2005;10:40-68
Gilman et. al., Nat Neurosci 2012;15:1723-1728

Blau = Gene mit Copy-Anzahl-Varianten
Grün = Gene mit De Novo Einzelnukleotidvariationen
Rot = Gene aus Genom-weiten Assoziationsstudien
Graue Striche = Hohe Wahrscheinlichkeit, dass die verbundenen Gene eine ähnliche Funktion haben
How does neurobiology “act” in schizophrenia?

Genetic alterations
- Multitude of potentially affected genes
- Mostly involved in neurodevelopment

Environmental factors

Epigenetic factors

Increased vulnerability
- Subtle changes of brain structure and/or brain function

Psychological factors

Social factors

First episode

Progress of structural and/or functional brain alterations

Infections
Toxins (cannabis, …)
Modular concept of the pathophysiology of mental disorders

**Pro**
- Individual diagnostics, i.e. individual hierarchy of module dysfunction
- All disorders are described in terms of affected functional modules
- Module-oriented treatment

**Contra**
- Uneasy and expensive
- Lack of taxonomy
- Lack of normal values

**Biological?**
- cognitive
- emotional
- social
- affective
- perceptive
- intentional
- motor

**Psychosocial?**

**Dysfunctional Profile?**

**Functional Diagnostics**
- Modular Tx

**Module**
- Psychosis
- Module
Empirical evidence for disturbed modularity in schizophrenia

<table>
<thead>
<tr>
<th>Key Findings</th>
<th>Method</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Reduced local clustering and integration of functional networks in a working memory task in people with schizophrenia ( n = 20 ).</td>
<td>Task-related EEG, graph theoretical analysis</td>
<td>44</td>
</tr>
<tr>
<td>Disrupted small-world network topology in people with schizophrenia ( n = 31 ): increase of path length and decrease of connectivity correlated with illness duration.</td>
<td>Resting-state fMRI, graph theoretical analysis</td>
<td>41</td>
</tr>
<tr>
<td>Significantly reduced modularity in childhood-onset schizophrenia ( n = 13 ) due to reduced density of intramodular connections between neighboring regions</td>
<td>Resting-state fMRI, graph theoretical analysis</td>
<td>43</td>
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<tr>
<td>Lower clustering and shorter pathlengths in patients with schizophrenia ( n = 40 )</td>
<td>Resting-state scalp EEG</td>
<td>45</td>
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<tr>
<td>Less hierarchical organization of brain network in schizophrenia ( n = 203 ), increased mean connection distance and increased clustering</td>
<td>Structural MRI, interregional correlation of gray matter volume</td>
<td>46</td>
</tr>
<tr>
<td>Longer node-specific pathlengths and less centrality in frontal hubs in people with schizophrenia ( n = 40 )</td>
<td>Diffusion tensor imaging and magnetization transfer ratio assessment of brain MRI, graph theoretical analysis</td>
<td>47</td>
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<td>Decreased strength of functional connectivity, reduced clustering and small-worldness in people with schizophrenia ( n = 12 )</td>
<td>fMRI functional connectivity and functional network metrics analyses</td>
<td>42</td>
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</tbody>
</table>

Note: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging.

Gaebel and Zielasek, Schizophr Bull 2011; 37 S2: S5-S12.
An Integrated Model of Schizophrenia

Psychopathology

Brain Structure and Function

Behaviour

Genes

Determinants?
paranoid
disorganized
catatonia

Cognitive Factors:
- Attribution Biases
- Reasoning Styles
- Aberrant Salience
- Jumping to Conclusions
- Premorbid IQ

Divide:
- Pathogenic, Pathoplastic and Sustaining Factors

Experience, Learning

Environmental Modifiers (e.g., social isolation)

„Appraisal“

„Vulnerable individual“

„Epigenetics“

Connectivity Network Analysis

Neuropsychological Tests
- Functional and structural neuroimaging
- EEG, evoked potentials etc.

Concepts of mental disorders – SFB Workshop May 20, 2014
Etiopathogenesis and pathophysiology of mental disorders: Current areas of research

- Neurocognition, social cognition
- Endophenotypes
  - Sensorimotor processing
    - Pre-pulse inhibition
    - Suppression of P50
  - Eye movement dysfunctions
    - Smooth gaze pursuit
  - Working memory
    - Neuropsychological tests
    - fMRI
  - Structural brain alterations
    - Ventricular enlargement, regional atrophies
    - Altered gyrification
  - Late evoked potentials
    - P300 Oddball-Paradigma

- Functional neuroimaging, tractography, brain spectroscopy
- Genetic and epigenetic markers
- Pharmacogenotyping
- Etc.

Do we really understand how these processes act in mental disorders?
The concept of target symptoms in psychiatric treatment ...

So stand von Anfang an fest, daß es sich nicht um spezifische Therapien für bestimmte psychiatrische Krankheiten handelte, sondern um spezifische Einwirkungen auf psychopathologische Funktionsstörungen, wie sie bei einer Vielzahl psychiatrischer Krankheitsbilder therapeutisch im Mittelpunkt stehen.

Freyhan 1957

Right from the start it was certain that this was not a matter of specific therapies for specific psychiatric diseases, but rather a matter of specific actions on psychopathological dysfunctions which take center stage in a multitude of psychiatric clinical pictures.
Syndrome- and not disorder-oriented therapy

- Bewusstseinsstörungen
- Orientierungsstörungen
- Aufmerksamkeits- und Gedächtnisstörungen
- Formale Denkstörungen
- Befürchtungen und Zwänge
- Wahn
- Sinnestäuschungen
- Ich-Störungen
- Störungen der Affektivität
- Antriebs- und psychomotorische Störungen
- Circadiane Besonderheiten
- Andere Störungen (z.B. Suizidalität)

Antipsychotic Therapy

- Depressive Syndrome
- Paranoid-halluzinatory Syndrome
- Schizophrenia
- Delusional Depression
Phase-dependency of therapeutic goals

Prodromal Phase

Decompensation psychotic

Fully developed positive symptoms

Acute Phase

Transition

Stabilisation phase

Partial Response

Partial Remission

Response

Remission

Relapse

Negative symptoms

Initiation of Tx

Response

Remission

Recovery

Non-Response

Stable Phase

Initiation of Tx

Gaebel, Pharmacopsychiatry 2004, 37 Suppl 2, S90-S97
Table 2. Neural Circuit Disorders and Postulated Circuit Dysfunction

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Circuit</th>
<th>Postulated Circuit Dysfunction</th>
<th>DBS Target(s) Being Studied or that Could Be Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease, essential tremor, and dystonia</td>
<td>Motor</td>
<td>Beta and theta oscillations, GPI overactivity, STN overactivity, and neuronal bursting</td>
<td>STN, GPI, GPe, VL thalamus, PPN, and spinal cord</td>
</tr>
<tr>
<td>Major depression</td>
<td>Limbic</td>
<td>Increased activity in OFC, SCC, amygdala, and VS, failure to downregulate amygdalar activation</td>
<td>SCC, NAcc, habenula, and medial forebrain bundle</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>Motor/limbic</td>
<td>OFC hyperactivity and failure of VS-mediated thalamofrontal inhibition</td>
<td>NAcc, ITP, ALIC, and STN</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>Auditory</td>
<td>Sensory deafferentation, thalamocortical dysrhythm</td>
<td>Auditory pathways</td>
</tr>
<tr>
<td>Tourette’s syndrome</td>
<td>Motor/limbic</td>
<td>Overactive direct pathway, failure of thalamocortical inhibition</td>
<td>GPI and CM-PI</td>
</tr>
<tr>
<td>Schizophrenia—positive symptoms</td>
<td>Executive function, cognitive, and reward</td>
<td>Thalamocortical dysrhythm, failure of saliency networks</td>
<td>Temporal cortex and NAcc</td>
</tr>
<tr>
<td>Schizophrenia—negative symptoms</td>
<td>Motivation, reward, cognitive, and mood</td>
<td>Mesolimbic/mesocortical dysfunction, failure to engage anticipatory hedonic system</td>
<td>NAcc, VTA, and SCC</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Cognitive and memory circuits</td>
<td>Beta amyloid plaques throughout the brain, DMN dysfunction, cholinergic degeneration, and entorhinal cortex and hippocampal atrophy</td>
<td>Fornix, entorhinal cortex, hippocampus, cingulate, precuneus, frontal cortex, and nucleus basalis</td>
</tr>
<tr>
<td>Pain (phantom pain, deafferentation pain, central pain, and nociceptive pain)</td>
<td>Sensory systems and interoceptive awareness</td>
<td>Sensory deafferentation and abnormal neuronal spontaneous bursting behavior</td>
<td>Sensory pathways, periventricular/periaqueductal areas, and cingulate insula</td>
</tr>
<tr>
<td>Addiction</td>
<td>Reward</td>
<td>NAcc sensitivity to reward</td>
<td>NAcc</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Reward and mood</td>
<td>Frontoparietal disconnection, parietal hypometabolism, insular abnormality, and SCC overactivity</td>
<td>SCC and NAcc</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Various</td>
<td>Abnormal excitability and synchrony</td>
<td>CM thalamus, anterior thalamic nucleus, thalamus, and seizure focus</td>
</tr>
</tbody>
</table>

GPI, globus pallidus internus; GPe, globus pallidus externus; VL, ventrolateral; OFC, orbitofrontal cortex; VS, ventral striatum; NAcc, nucleus accumbens; DLPFC, dorsolateral prefrontal cortex; ITP, inferior thalamic peduncle; ALIC, anterior limb of internal capsule; CM-PI, centromedian-parafascicular; VTA, ventral tegmental area; DMN, default mode network; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; SCC, subcallosal cingulate.
## Research Domain Criteria (RDoC)

**NIMH Strategic Plan (Strategy 1.4):** “Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures.”


<table>
<thead>
<tr>
<th>Domain</th>
<th>Construct</th>
<th>Neurocircuitry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Affect</td>
<td>Fear/extinction Stress/Distress Aggression</td>
<td>Amygdala, Hippocampus, vmPFC, HPA axis, cortisol</td>
</tr>
<tr>
<td>Positive Affect</td>
<td>Reward Seeking Reward/Habit Learning</td>
<td>Mesolimbic dopamine pathways, OFC, Thalamus, Dorsal striatum</td>
</tr>
<tr>
<td>Cognition</td>
<td>Attention, Perception, Working Memory; Declarative Memory</td>
<td>Dorsolateral PFC, ACG, Medial and Lateral PFC</td>
</tr>
<tr>
<td></td>
<td>Language/behavior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cognitive (effortful) control</td>
<td></td>
</tr>
<tr>
<td>Social Processes</td>
<td>Imitation, Theory of Mind, Social dominance, Facial expression identification, Attachment/separation fear, Self-representation areas</td>
<td>Distributed cortical, Mesolimbic dopamine, Fusiform gyrus, ACC, insula</td>
</tr>
<tr>
<td>Arousal/regulatory processes</td>
<td>Arousal &amp; regulation (multiple)</td>
<td>Raphe nuclei, Locus coeruleus, Resting state network</td>
</tr>
</tbody>
</table>
Research Domain Criteria (RDoC)

The final specification for each construct will consist of:

• A definition of the construct’s functional aspects, summary of relevant circuitry, and relationship to other constructs;

• A list of current state-of-the art measures, paradigms, and procedures at each level of analysis;

• Current pressing research questions and issues pertaining to the construct, including one or two salient examples of the groupings of DSM/ICD categories that might be included in studies addressing these questions.

Neurobiology and Classification of Schizophrenia: Future Quests

1. Elucidate how genetic alterations and other vulnerability factors lead to neural network dysfunctions and altered brain protein expression

2. Determine how neural network dysfunctions are best assessed → „Endophenotypes“? „Connectome analyses“? „Transcriptome analyses“?

3. Show how these lead to psychological dysfunctions and psychopathological symptoms

Concepts of mental disorders – SFB Workshop May 20, 2014
Diagnostics and classification of mental disorders: the human factor – implicit disorder models

• Presentation of a schizophrenia case vignette
• Analysis of how frequently the following disorder model were used

<table>
<thead>
<tr>
<th>Models</th>
<th>CMHT Group</th>
<th>Medical</th>
<th>Social</th>
<th>Cognitive-behavioural</th>
<th>Psycho-therapeutic</th>
<th>Family</th>
<th>Conspiratorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatrists</td>
<td></td>
<td>91.3</td>
<td>7.9</td>
<td>11.8</td>
<td>5.4</td>
<td>6.3</td>
<td>17.1</td>
</tr>
<tr>
<td>Social workers</td>
<td></td>
<td>8.8</td>
<td>47.5</td>
<td>7.5</td>
<td>36.7</td>
<td>1.3</td>
<td>21.6</td>
</tr>
<tr>
<td>Community nurses</td>
<td></td>
<td>60.8</td>
<td>25.1</td>
<td>13.3</td>
<td>19.6</td>
<td>0.0</td>
<td>20.4</td>
</tr>
<tr>
<td>Patient Group 1</td>
<td></td>
<td>60.7</td>
<td>29.8</td>
<td>8.3</td>
<td>26.2</td>
<td>0.0</td>
<td>26.2</td>
</tr>
<tr>
<td>Patient Group 2</td>
<td></td>
<td>-4.5</td>
<td>41.0</td>
<td>7.7</td>
<td>46.8</td>
<td>0.0</td>
<td>27.6</td>
</tr>
<tr>
<td>Informal carers</td>
<td></td>
<td>43.3</td>
<td>18.8</td>
<td>22.1</td>
<td>7.1</td>
<td>24.2</td>
<td>18.8</td>
</tr>
<tr>
<td>Mean % support for model</td>
<td></td>
<td>43.4</td>
<td>28.4</td>
<td>11.8</td>
<td>23.6</td>
<td>5.3</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Main result: Every group had a multitude of implicit disorder models, which may influence diagnostic or therapeutic decision making

Diagnostics and classification of mental disorders: the human factor – „natural taxonomies“?

- WHO-study in 517 psychiatrists, psychologists and other health care personnel in the area of mental disorders
- Participants from eight countries (Brazil, China, India, Japan, Mexico, Nigeria, Spain and the U.S. A.)
- Sorting task to detect hierarchical order of mental disorder (criterion: similarity of the clinical pictures or similar therapy)

Main result: The „natural“ taxonomies were similar globally and were not only influenced by the preferred classification system „Shallow“ taxonomies were preferred and clustering of mental disorders into higher order groups was often dismissed
Current challenges in the diagnostics and classification of mental disorders

- How can nosological entities be defined given the complexity of the etiopathogenesis and pathophysiology of mental disorders? Which methods of validation are to be used?

- How can neurobiological factors be integrated into classification procedures?

- How can the border between „still healthy“ and „already ill“ be better defined, for example for prodromal states of mental disorders?

- Should and – if so, how - could comorbidity be reduced?

- Which integrative concept of mental disorders is the best to reflect the complexity of mental disorders?
What classification systems for mental disorders will need to consider...

• **Etiopathogenesis and pathophysiology** of mental disorders are not yet elucidated

• There are no valid **biomarkers** for mental disorders

• Clinical classification of mental disorders is still useful – to provide information about prognosis, treatment and research

• Including **dimensional** – syndrome-oriented – classification systems seems to be a compromise while research is on its way towards „proving“ mental disorders
Thank you for your attention
Vielen Dank für Ihre Aufmerksamkeit!