LVR Klinikum Düsseldorf – Kliniken der Heinrich-Heine-Universität Düsseldorf

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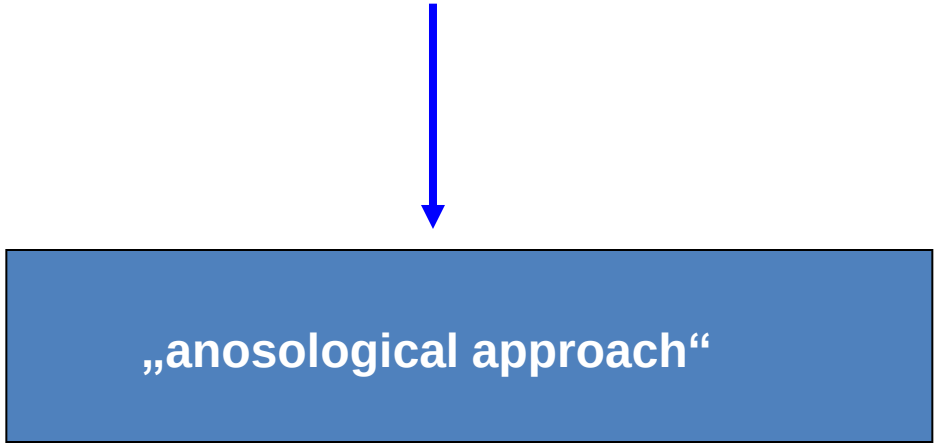
Concepts of mental disorders

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

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



Distinct pathophysiological processes

initiate

Preformed patterns of reactions under given circumstances

lead to

Symptoms and Syndromes

Nach P. Hoff: Nosologische Grundpostulate bei Kraepelin
Z Klin Psychol Psychopathol Psychother 1988;36: 328-336

Early proposal of an a-nosological diagnostic approach

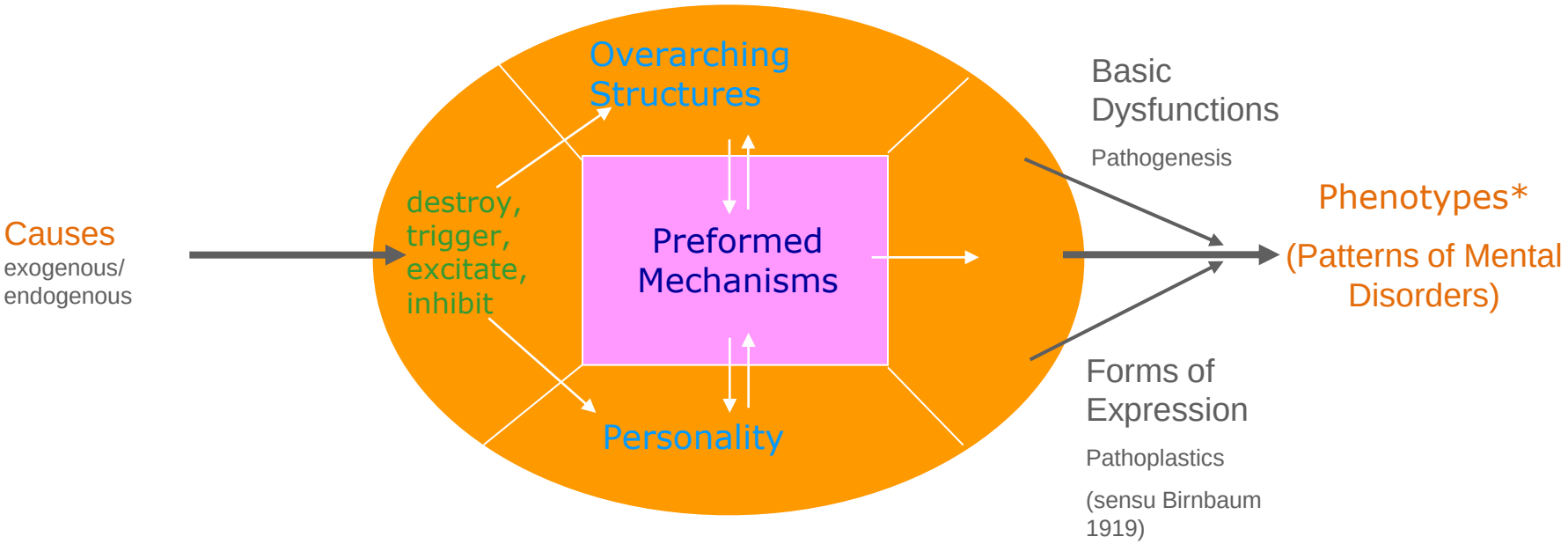
Die ‚Erscheinungsformen des Irreseins' sind die ‚natürliche Antwort der menschlichen Maschine', die ‚auf das Spiel vorgebildeter Einrichtungen unseres Organismus' durch Beeinträchtigung ‚gleicher Gebiete' zurückgehen.

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



Developmental concepts of phylogenesis and ontogenesis

*Analogous to Bonhoeffers 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)

	ICD-10 F20	DSM-III-TR 295.x
Sensitivity	*64%*	*51%*
Spezifity	*89%*	*93%*
pos.präd.Value	*82%*	*83%*
neg, präd. Value	*77%*	*73%*

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 Krankheitsentitäten 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**)

Potuzak et al., Compr Psychiatry 2012; 53(8):1118-29.

	Hallucinations	Delusions	Disorganized Speech	Abnormal Psycho-motor Behavior	Negative Symptoms	Impaired Cognition	Depression	Mania
0	Not Present	Not Present	Not Present	Not Present	Not Present	Not Present	Not Present	Not Present
1	Equivocal (severity or duration not sufficient to be considered psychosis)	Equivocal (severity or duration not sufficient to be considered psychosis)	Equivocal (severity or duration not sufficient to be considered disorganization)	Equivocal (severity or duration not sufficient to be considered abnormal psychomotor behavior)	Equivocal decrease in facial expressivity, prosody, gestures or self-initiated behavior	Equivocal (cognitive function not clearly outside the range expected for age or SES, i.e., **within 0.5 SD of mean**)	Equivocal (occasionally feels sad, down, depressed or hopeless; concerned about having failed someone or at something but not preoccupied)	Equivocal (occasional elevated, expansive, or irritable mood or some restlessness)
2	Pres… mild… pres… upon… very… by v…				…e	Present, but mild (some reduction in cognitive function; below expected for age and SES, **0.5-1 SD from mean**)	Present, but mild (frequent periods of feeling very sad, down, moderately depressed or hopeless; concerned about having failed someone or at something with some preoccupation)	Present, but mild (frequent periods of somewhat elevated, expansive or irritable mood or restlessness)
3	Pres… mod… pres… resp… voic… som… both… voic…	…beliefs)			…behavior	Present and moderate (clear reduction in cognitive function; below expected for age and SES, **1-2 SD from mean**)	Present and moderate (frequent periods of deep depression or hopelessness; preoccupation with guilt, having done wrong)	Present and moderate (frequent periods of extensively elevated, expansive, or irritable mood or restlessness)
4	Present and severe (severe pressure to respond to voices, or is very bothered by voices)	Present and severe (severe pressure to act upon beliefs, or is very bothered by beliefs)	Present and severe (speech almost impossible to follow)	Present and severe (abnormal or bizarre motor behavior or catatonia almost constant)	Present and severe decrease in facial expressivity, prosody, gestures or self-initiated behavior	Present and severe (severe reduction in cognitive function; below expected for age and SES**, > 2SD from mean**)	Present and severe (deeply depressed or hopeless daily; delusional guilt or unreasonable self-reproach grossly out of proportion to circumstances)	Present and severe (daily and extensively elevated, expansive, or irritable mood or restlessness)

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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DSM-5: Definition Mental Disorder"

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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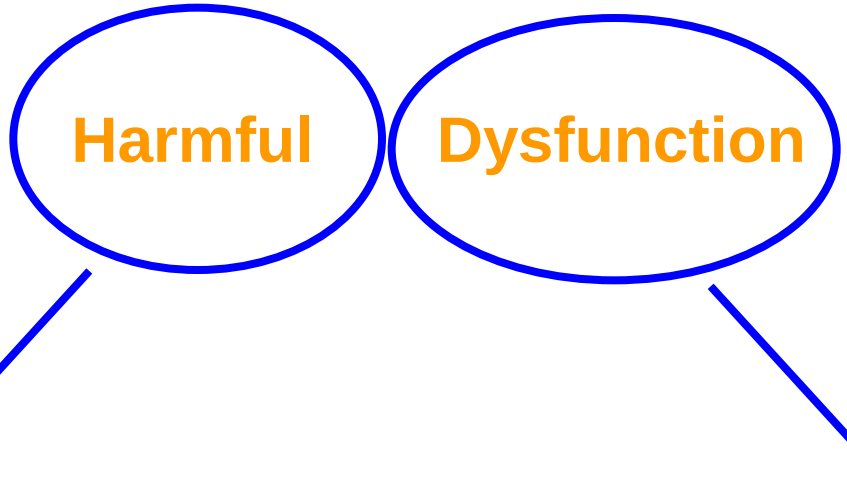
Wakefield´s Concept of „Harmful Dysfunction“



„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

Wakefield JC, The concept of mental disorder: diagnostic implications of the harmful dysfunction analysis. World Psychiatry 2007; 6: 149-156

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

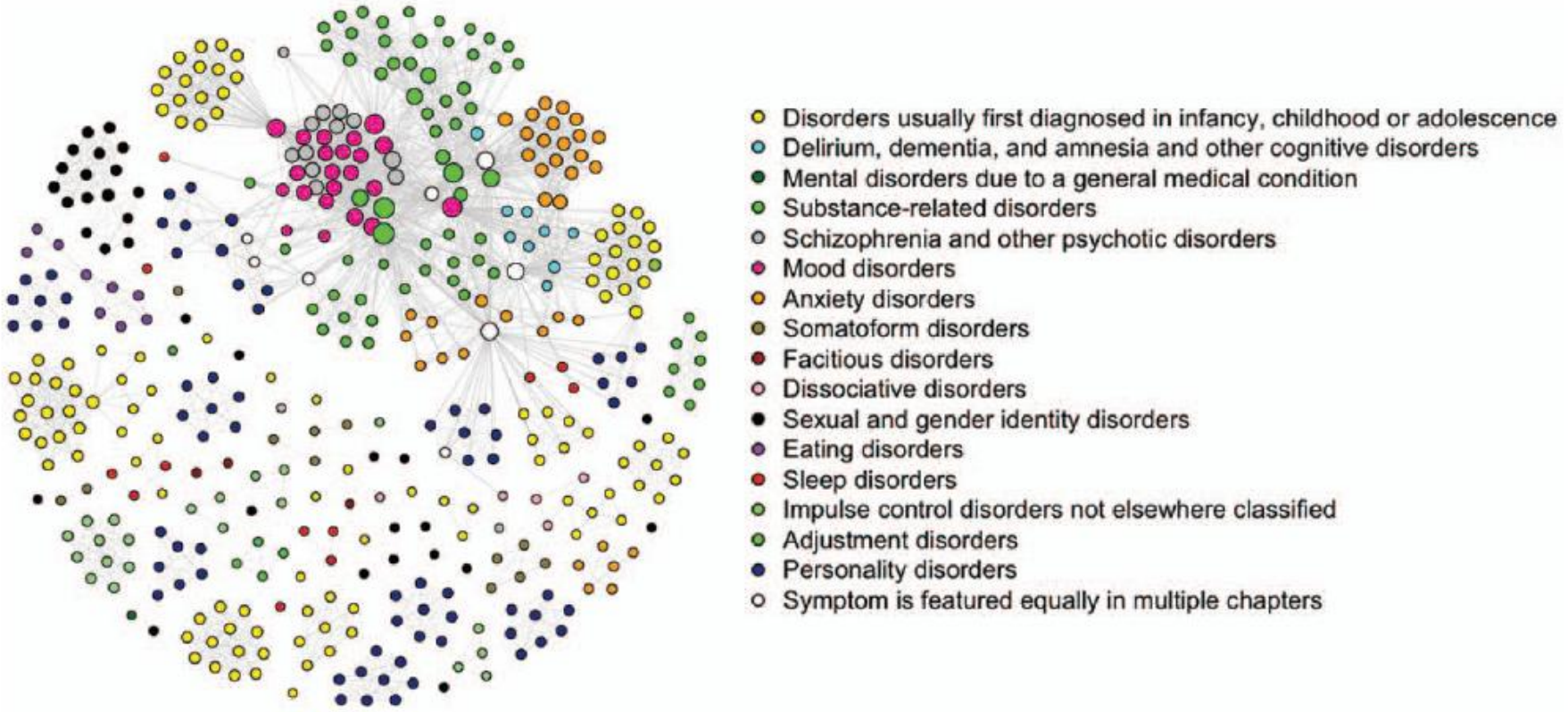
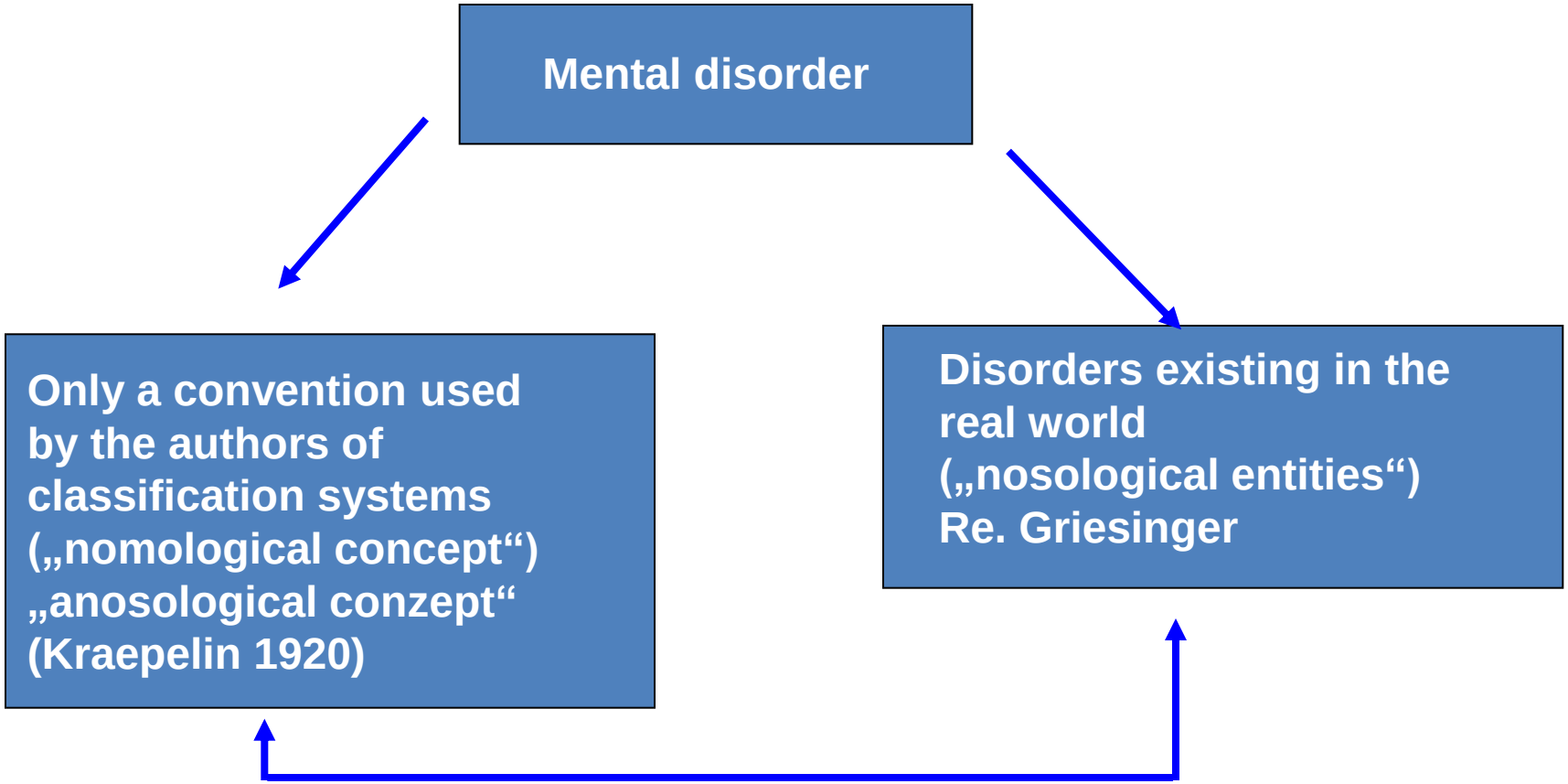


Figure 2. The DSM-IV symptom space. Symptoms are represented as nodes and connected by an edge whenever they figure in the same disorder. Color of nodes represents the DSM-IV chapter in which they occur most often.
doi:10.1371/journal.pone.0027407.g002

Borsboom D et al., PloS ONE 6(11):e27407. DOI:10.1371/journal.pone.0027407 (2011).

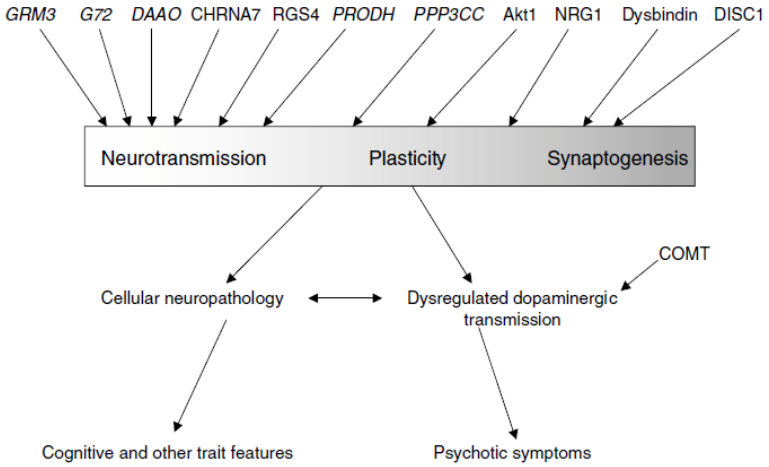
Mental disorders – only a convention or correlate of a real disorder?



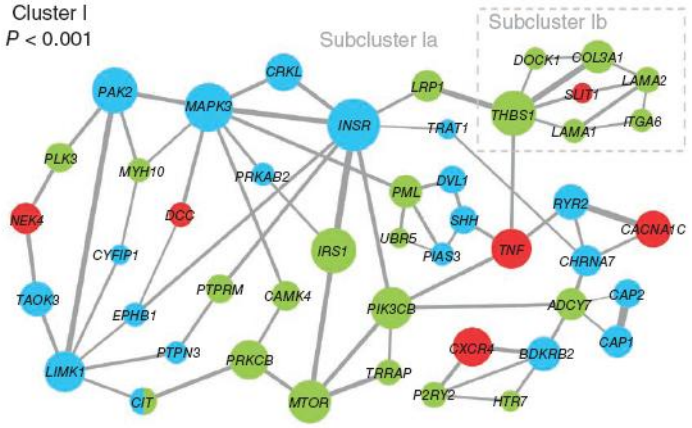
Is there a real world correlate of any mental disorder?

Etiopathogenesis of schizophrenia

- Approximately 850 risk loci
- Considerable overlap with other disorders
- None of the associations suitable for individual diagnostics or classification



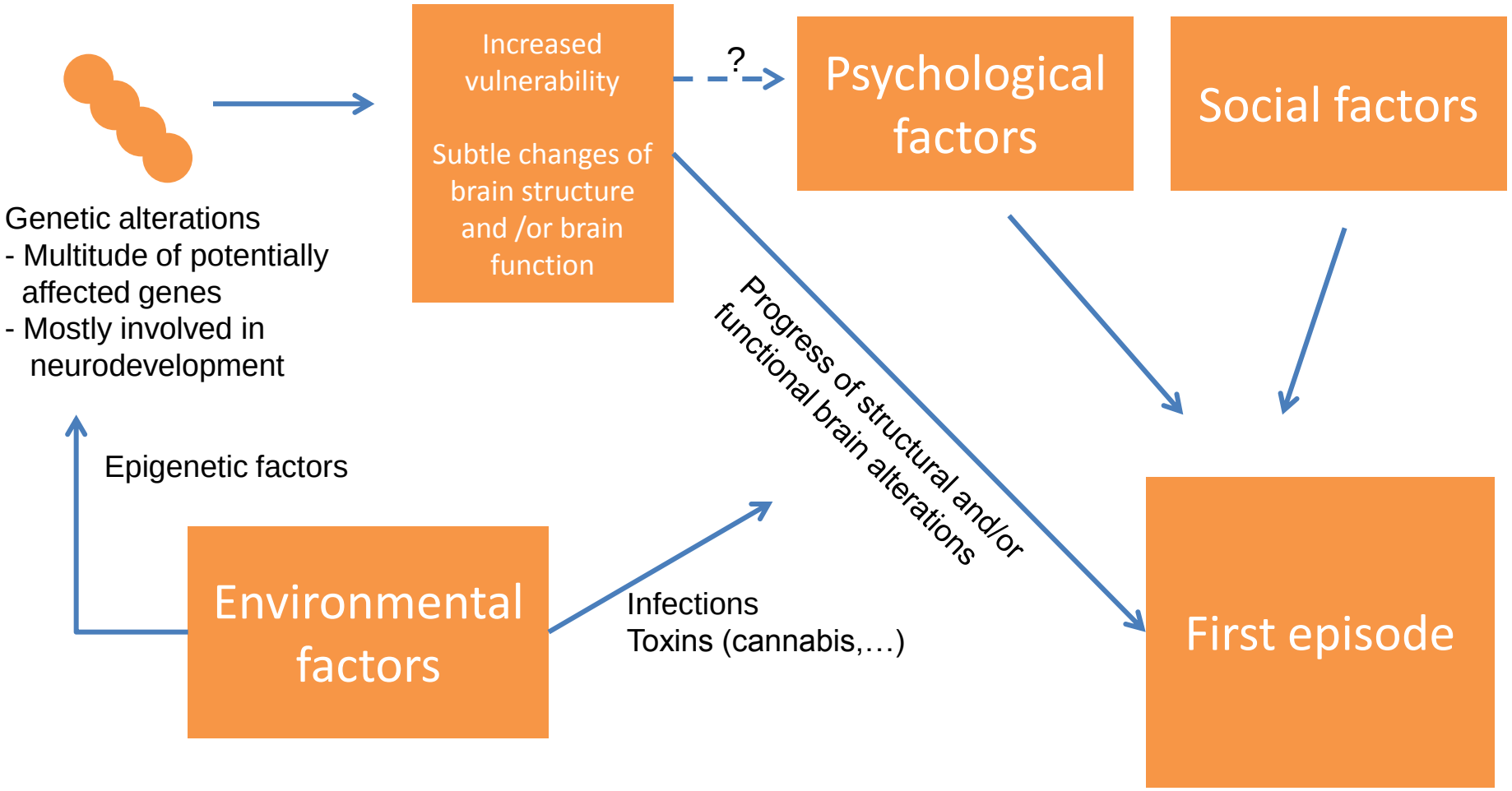
Harrison & Weinberger, Mol Psychiatry 2005;10:40-68



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

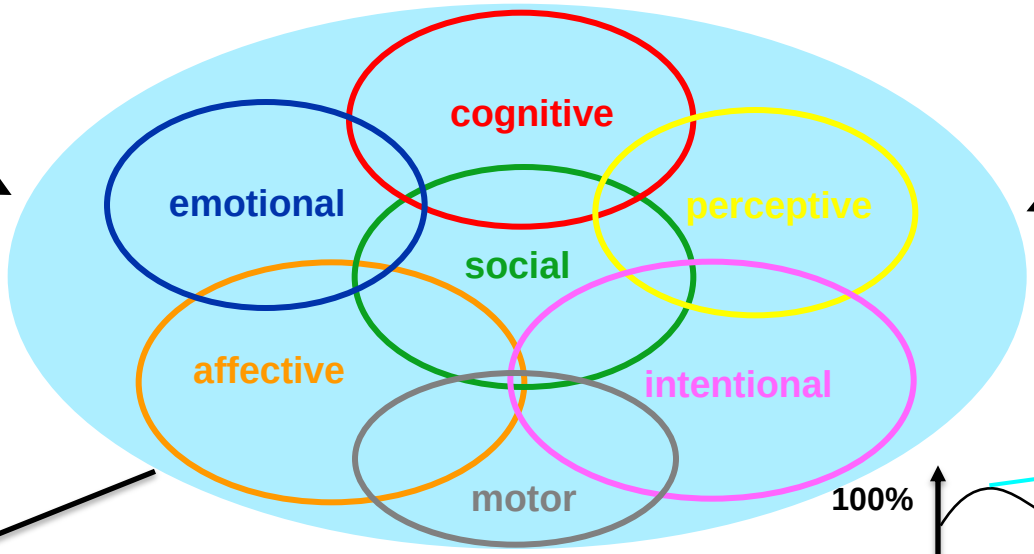
How does neurobiology "act" in schizophrenia?



Modular concept of the pathophysiology of mental disorders

Biological?

Psychosocial?

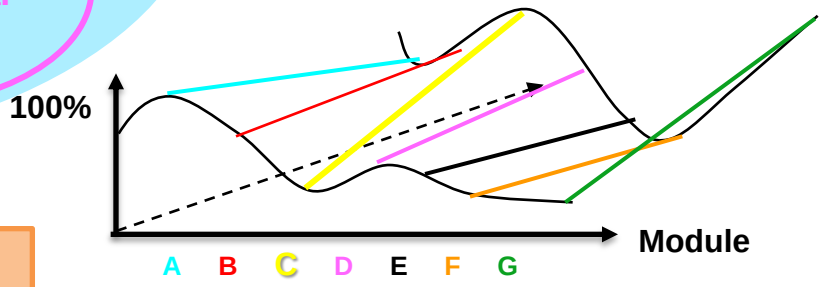


Dysfunctional Profile?

Functional Diagnostics

↓

Modular Tx



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

Empirical evidence for disturbed modularity in schizophrenia

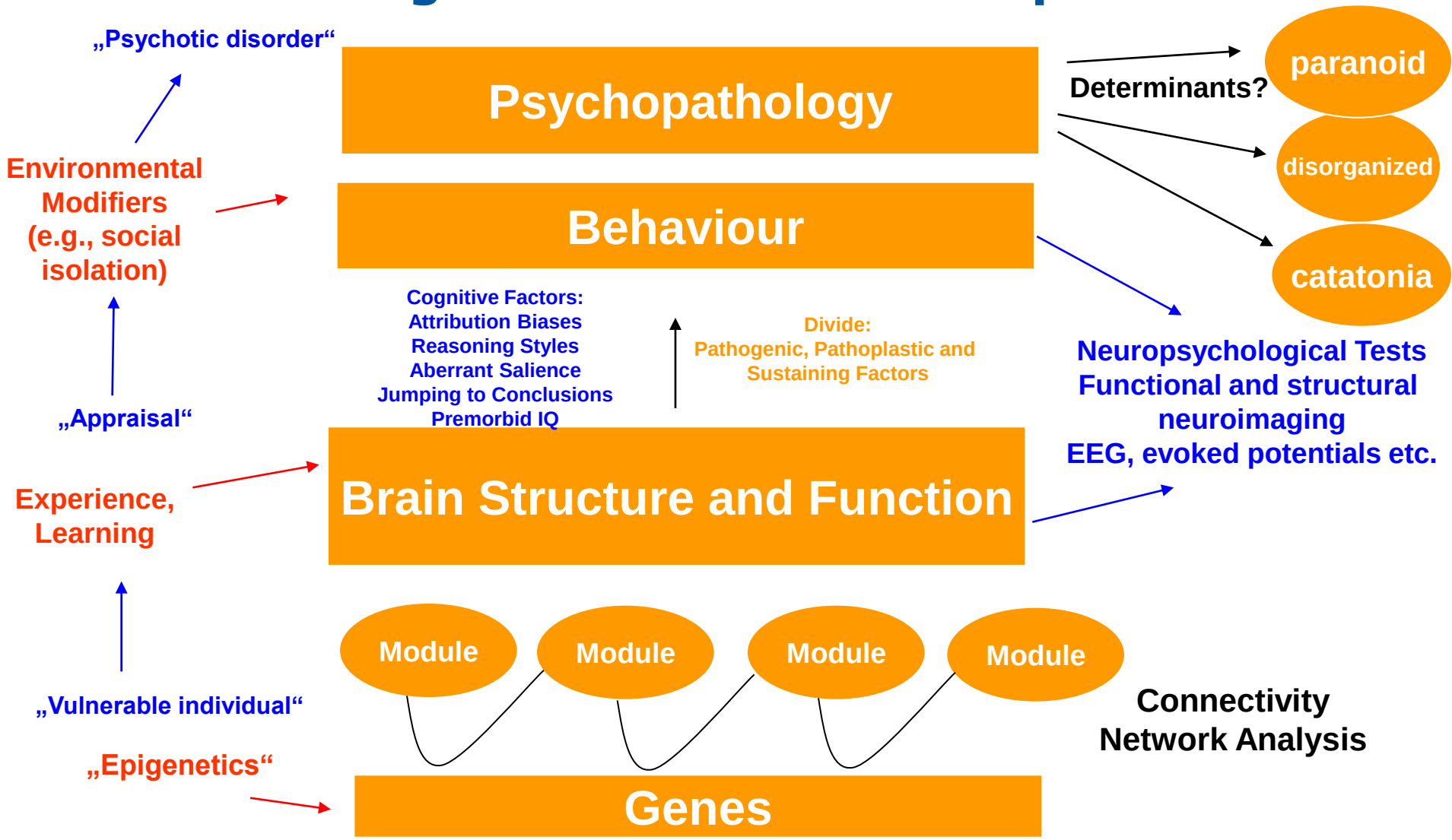
Table 1. Empirical Evidence for Disturbed Modularity in Patients With Schizophrenia

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

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



Etiopathogenesis and pathophysiology of mental disorders: Current areas of research

- Neurocognition, social cognition
- Endophenotypes
  - Sensorimotor processing
    - Pre-pulse inhhibition
    - 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 theses processes act in mental disorders?

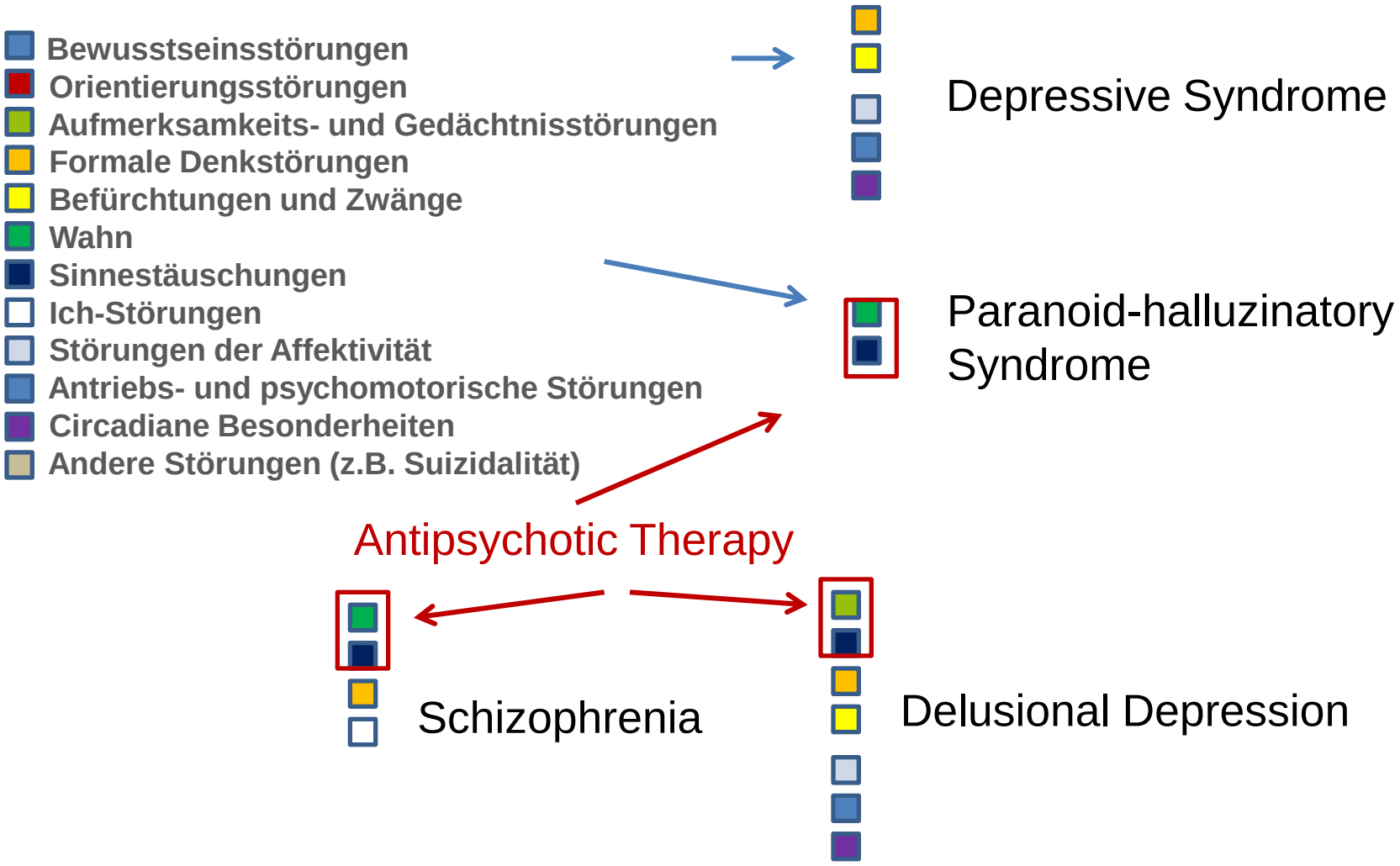
The concept of target symptoms in psychiatric treatment ...

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.

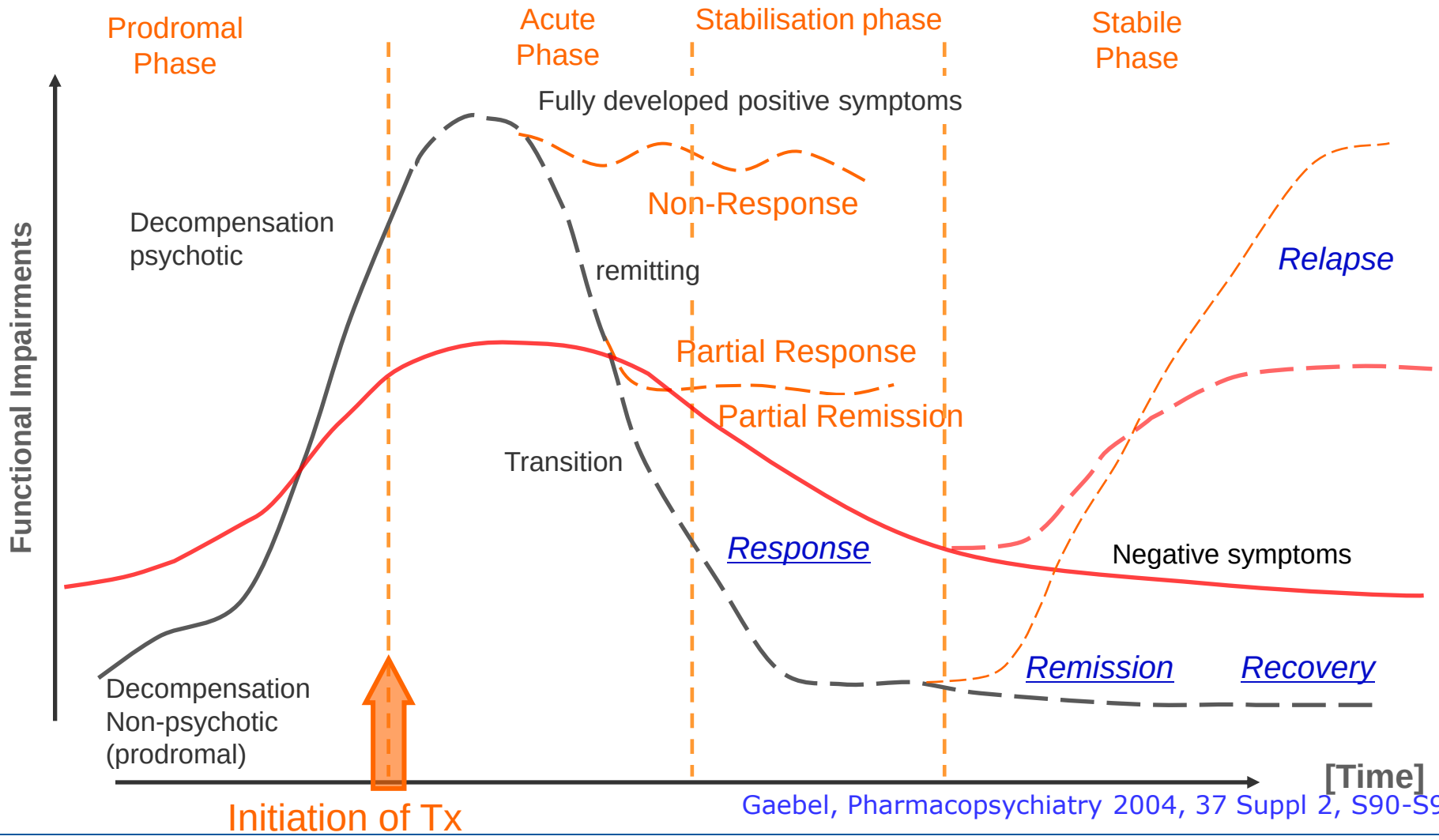
Freyhan 1957

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



Phase-dependency of therapeutic goals



Gaebel, Pharmacopsychiatry 2004, 37 Suppl 2, S90-S97

Reported neurocircuit dysfunctions in mental disorders

Table 2. Neural Circuit Disorders and Postulated Circuit Dysfunction

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

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-Pf: centromedian-parafascicular; VTA, ventral tegmental area; DMN, default mode network; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; SCC, subcallosal cingulate.

Lozano & Lipsman, Neuron 2013;77:406-424

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."*
http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml#strategic-objective1

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

http://www.nimh.nih.gov/research-funding/nimh-research-domain-criteria-rdoc.shtml

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.

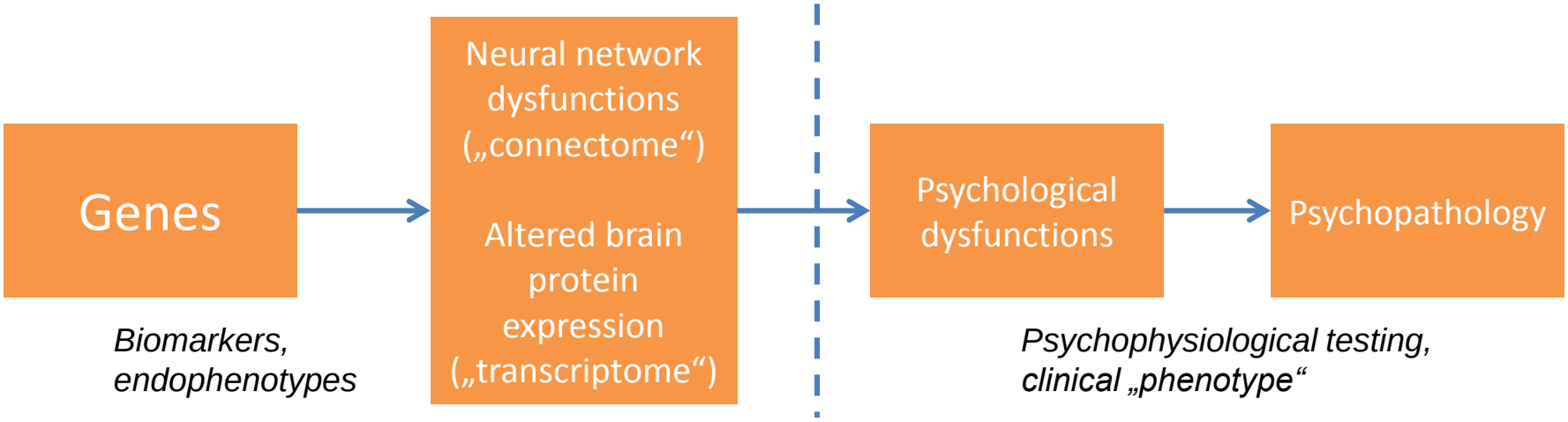
http://www.nimh.nih.gov/research-funding/nimh-research-domain-criteria-rdoc.shtml

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



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 2
Percent of each multi-agency group whose responses agreed with the model

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

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

Colombo A et al., Soc Sci Med 2003;56:1557-1570

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

Reed GM et al., J Clin Psychol 2013; DOI 10.1002/jclp.22031

Current challenges in the diagnostics and classification of mental disorfders

- 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 !