The case for a differentiated nosology of the endogenous psychoses

Prof. Dr. Gerald Stöber

Department of Psychiatry and Psychotherapy
University of Würzburg, Germany
stoeber_g@klinik.uni-wuerzburg.de

Classification of the endogenous psychoses

	favourable prognosis			*unfavourable prognosis*	
Kraepelin	manic-depressive insanity			dementia praecox	
Bleuler	manic-depressive illness	group of schizophrenias			
DSM-IV ICD 10	affective disorders	schizoaffective disorders			schizophrenia
Leonhard	monopolar affective psychoses	manic-depressive illness	cycloid psychoses	unsystematic schizophrenias	systematic schizophrenias

Descriptive clinical phenomenology of distinct psychic levels

qualitative and quantitative disturbances

- **Affectivity**
- **Thinking**
- **Psychomotility - Activity („Antrieb“; „Wollen“)**

descriptive psychopathology

↓

symptom connections

(„Symptomverbindungen“)

cardinal symptoms / core disturbances

facultative symptoms

↓

clinical entities

(„Krankheitsgruppierungen“)

↓

nosology of psychic diseases

differentiated aetiology

Basic diagnostic differences between ICD-10/DSM-IV and Leonhard‘s nosology

DSM-IV / ICD-10

Diagnosis is made by the appearance of a **minimum number of symptoms** from a given symptom-catalogue which have to exist over a **given period of time.**

Leonhard‘s nosology

Diagnosis is made by the evidence of **specific symptom constellations (specific symptoms** form **characteristic syndromes),** which run a **typical course (prognosis).**

The „atypical psychoses“: challenge in psychiatric nosology

Kraepelin‘s dichotomy of the endogenous psychoses

Manic Depression ↓ **Schizophrenia**

“atypical psychoses”

bouffée délirante (Magnan)
schizophreniform disorders (Langfeldt)
atypical psychoses (Mitsuda)
„cases in-between“ (Schneider)
schizoaffective psychoses (Kasanin)

→ non-distinctive symptomatology due to

- diversity of clinical symptoms (affective, psychotic and “schizophrenic” symptoms)

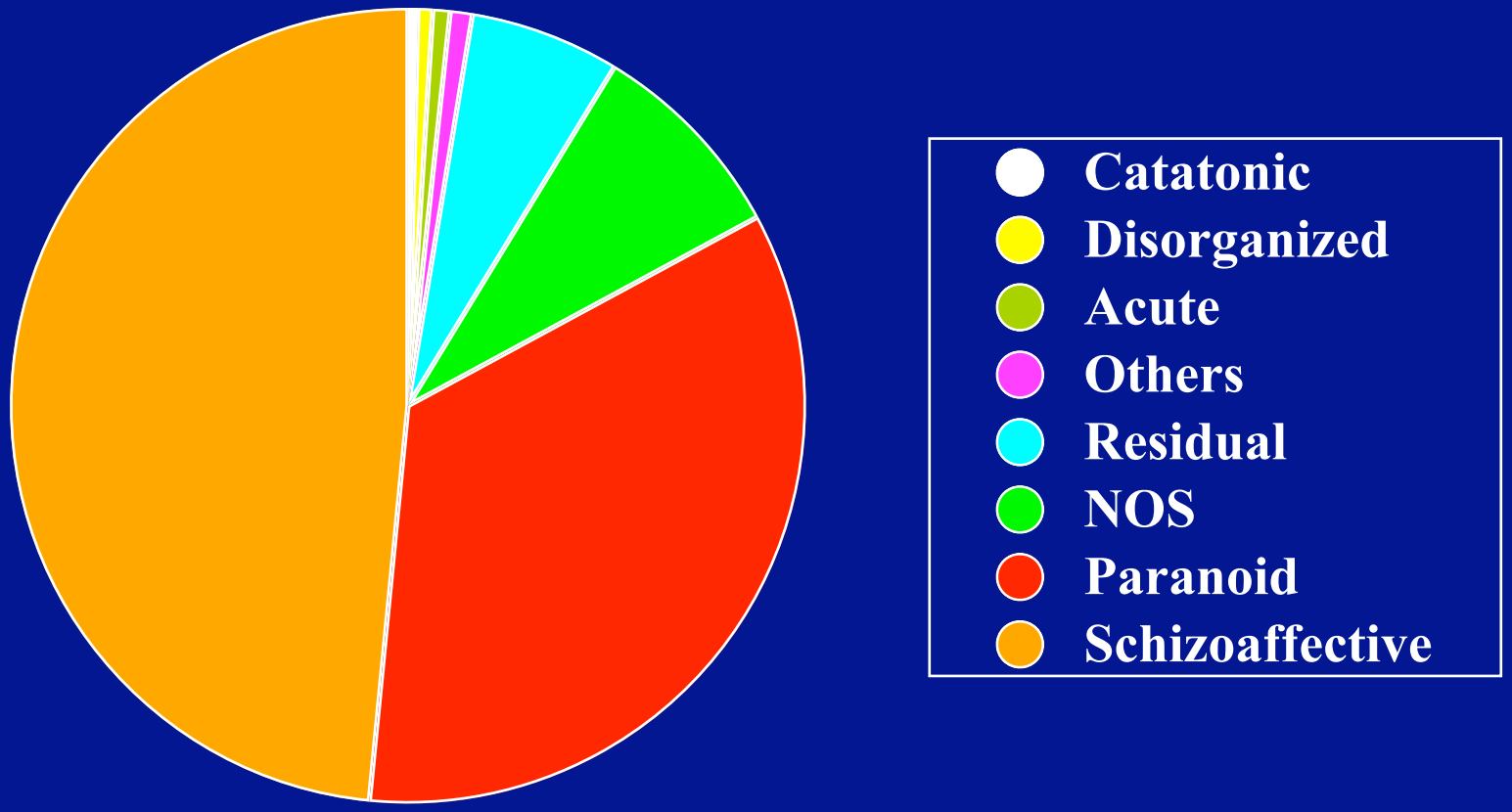
- episodic/phasic course (full recovery) versus

tendency towards sustained dysfunction (unfavourable long-term course)

Potential solutions for the problem of the „atypical psychoses“

- ***broadening*** of the ***diagnostic criteria*** for either schizophrenia or manic-depression lowering the clinical ***validity*** and ***heuristic value*** of both diagnostic categories.
- implementation of a category of ***„mixed psychosis“*** including elements of both schizophrenic and (bipolar) affective psychoses => ***schizoaffective psychosis***.
- delineation of ***nosologically independent phenotypes*** beyond the Kraepelinian dichotomy by applying criteria of a ***differentiated psychopathology and nosology***.

US-National Data on Schizophrenia Subtypes



year 2002
N = 272,000

http://hcup.ahrq.gov/HCUPnet.asp
SN Caroff, unpublished data, 2005

Schizoaffective Psychoses

KRAEPLIN
BEULER: „Mischpsychosen“

SCHNEIDER: „Zwischen-Fälle“

KASANIN:
Schizoaffective Psychosis

ANGST
CLAYTON: Schizoaffective Psychoses

modern concepts

- **a)**
  - **concurrent**
  - **concurrent and sequential**
- **b)**
  - **unipolar**
  - **bipolar**
- **c)**
  - **schizo-dominant**
  - **affect-dominant**

according to Maneros, 1995

The schizoaffective psychoses: an unsatisfying solution to the problem

- diagnosis comprises ***different and controversial conceptions***

- its commonly used conceptualisation as „mixed psychosis“ ***cannot account adequately for*** the ***symptomatology*** and ***course*** of „atypical psychoses“.

- lack of prognostic significance

- no or inconclusive findings regarding ***aetiology***

Cycloid psychoses in ICD-10 and DSM-IV

- **ICD-10:** „acute and transient psychotic disorders“ (ATPD)
  „non-organic psychosis NOS“
- ***DSM-IV***: „brief psychotic disorder“ (DSM-III-R „reactive“)
  „schizophreniform disorder“
  „psychotic disorder NOS“

Criticisms:

- superficial description of symptomatology
- arbitrary temporal criteria regarding onset and remission as diagnostic criteria

Acute polymorphic psychotic disorders (ICD 10): an alternative concept of cycloid psychoses?

- time criteria regarding onset: change from a non-psychotic to a „clearly psychotic state“ within ≤2 weeks.
- appearance of „multiple forms of hallucinations or delusional phenomena“, alternating in form and intensity from day to day or during the same day
- presence of an „alternating affective state“
- „typical symptoms of a schizophrenia“ (Schneiderian „first rank symptoms“)
- symptoms must not persist ≥1 month (schizophrenic symptoms) or ≥3 months (other symptoms) => switch of diagnosis (schizoaffective or psychosis NOS etc.)

→ Criticism: - no precise delineation of the symptomatology

- arbitrary time criteria for occurrence and remission of symptoms are decisive for diagnosis.

Atypical psychoses in view of a Leonhard‘s differentiated psychopathology

- **Subdivision of endogeneous psychoses into five distinct main groups of psychoses with their respective subforms permits a precise classification of virtually every manifestation of „atypical“ psychoses.**

- **The majority of „atypical“ psychoses represent forms of cycloid psychoses**

  that can be distinguished from affective psychoses and schizophrenic psychoses.

- **A fraction of „atypical“ psychoses can be identified as forms of unsystematic schizophrenias.**

Atypical psychoses in view of differentiated psychopathology

- existance of independent group(s) of endogenous psychoses in addition to affective and schizophrenic psychoses, i. e. the cycloid psychoses.
- from this point of view, cycloid psychoses are by no means simple mixed forms (i.e. schizoaffective psychoses), but are to be delineated from both affective and schizophrenic psychoses.
- this assumption is affirmed by epidemiological, clinico-genetic and biological findings
- suggesting cycloid psychoses as clinically and nosologically distinct entities

Cycloid Psychoses: Historical overview

MOREL: Degenerationskonzept

MAGNAN: Degenerationspsychose

EY: Bouffée délirante

WERNICKE: Motilitätspsychosen

Eingebungspsychosen

KLEIST: Phasische Psychosen

Zykloide Psychosen

MITSUDA: Atypische Psychose

HATOMANI: Periodische Psychose

SCHRÖDER: Metabolische Psychosen

LEONHARD: Zykloide Psychosen

(Komplettierung)

PERRIS: Zykloide psychotische Störung

(Vergröberung)

according to Perris, 1986

Classification of the Endogenous Psychoses in Differentiated Psychopathology

monopolar affective psychoses
manic-depressive disease

cycloid psychoses
- anxiety-happiness psychosis
- confusion psychosis
- motility psychosis

} **favourable prognosis**

unsystematic schizophrenias
- affect-laden paraphrenia
- cataphasia
- periodic catatonia

systematic schizophrenias
- systematic paraphrenias
- hebephrenias
- systematic catatonias

} **unfavourable prognosis**

Cycloid psychosis and unsystematic schizophrenias

psychic level	cycloid psychosis	unsystematic schizophrenias
affectivity	anxiety-happiness psychosis	affect-laden paraphrenia
thinking	confusion psychosis	cataphasia
psychomotility	motility psychosis	periodic catatonia

Cycloid Psychoses
General Criteria

- bipolarity with polymorphic symptomatology
- phasic course with complete remission after each episode
- absence of schizophrenic residual symptoms
- clinical subtypes affecting distinct psychic systems:

affectivity	anxiety-happiness psychosis
thought	excited-inhibited confusion psychosis
(psycho)-motility	hyperkinetic-akinetic motility psychosis

Cycloid psychosis
bipolar psychoses with characteristic syndromes

anxiety-happiness psychoses	confusion psychosis	motility psychosis
ecstacy ecstatic mood and feeelings of happiness with illusionary and hallucinatory experiences ecstatic ideas with altruistic components (religious ideas, social/political tasks) affective waves with ideaas of being called, elevated to a divine level or inspired by God	**excitation** incoherence of thought process with pressure of speech disgressive choice of theme ideas of significance or reference	**hyperkinesia** restless with increase of expressive and reactive motions distractility by momentary events in the enviroment with senseless motor activity
anxiety anxiety with distrust and ideas or reference, ideas of threat or presecution anxiety with paranoid features or hypochondriacal somatic sensations	**inhibition** inhibition of tought process with verbal improverishment perplexity and mutism ideas of significance or reference	**hypokinesia / aktinesia** rigid posture and facial expression disappearance of reactive motions reduction or standstill of voluntary movements
illusions or hallucinations closely related to ecstacy or anxiety	misidentification of persons acoustic or somatopsychic hallucinations	incoherent speech, unarticulated screaming mutism
rapid switches between anxiety and ecstasy	rapid affective fluctuations hallucinations, persecutory ideas	anxious/ecstatic mood swings, rapid alternation of both poles

Unsystematic schizophrenias
bipolar psychoses with characteristic syndromes

affect-laden schizophrenia	cataphasia	periodic catatonia
ecstacy with immense grandeur delusion of persecution misinterpretations, false perceptions acustic and somatic hallucinations systematization of delusions to absurd, fantastic ideas	**excitation** confused pressure of speech logical blunders and derailments wrong choice of words, neologisms, contaminations. „Wortsalat“ grammatical and semantic errors, paragrammatism	**hyperkinesia with akinetic traits** psychomotor excitement and restlessness with iterations, stereotypies parakinesia, facial grimacing distorted movements impulsive actions
irritated reference syndrome ideas of reference closely linked to affective irritation and affective fluctuations hostile reinterpretations of the environment somatic hallucinations and misperceptions coming from outside (machines, rays etc)	**inhibition** thought inhibition or mutism logical errors, syntactic and semantic errors ideas of reference numbing of reactivity, and facial expression blunted staring at the examiner	**hypokinesia with stereotypies, iterations** stupor with psychomotor negativism stiff motor activity bizarre, stereotype postures uniform movements perseveration
residual syndrome persistent, affectively anchored delusions or hallucinations overly sensitive, denying delusions loss of interest, blunted affectivity	**residual syndrome** persistent logical errors paralogic thinking (proverbs) behaviour remains sensible activities preserved with blunted, indifferent affectivity	**residual syndrome** psychomotor weakness of expressive movements, isolated stereotypies, grimacing facial movements, disharmoniously stiff or parakinetic movements and diminished incentive

Cycloid Psychoses: the clinical evidence

- reliable discrimination of the clinical syndromes from schizophrenic, schizoaffective and affective psychoses

(Perris 1974, Cutting et al. 1978, Brockington et al. 1986, Beckmann et al. 1990, Maj 1990, Pillmann et al. 2001, Peralta & Cuesta 2003, van der Heijden et al. 2004)

high diagnostic stability and prognostic validity

(Perris 1974, Brockington et al. 1982, Ungvari 1985, Maj 1988, Beckmann et al. 1990, Tolna et al. 2001)

high interrater-reliability of the diagnoses (Cohen's kappa 0.89)

(Franzek & Beckmann 1992, Pfuhlmann et al. 1996, Pfuhlmann et al. 2004)

Aetiology of the cycloid psychoses

complex multifactorial pathogenesis

- enviromental factors: early noxious events
  first trimester gestational infections; MPAs
- low genetic loading according to family and twin studies
  minor gene effects

Neurophysiology and Imaging

P300-peak and amplitude: normal topography and latency, significantly higher amplitude than in controls and schizophrenics (hyperarousal)

reversible acute hyperfrontality using ^{99m}Tc-HMPAO-SPECT

Differenzierte Therapieansätze bei zykloiden Psychosen

Akuttherapie: gute Response des paranoid-halluzinatorischen oder hyperkinetischen Syndroms auf Neuroleptika

syndromorientierte Behandlung der affektiven Schwankungen mit Antidepressiva und Benzodiazepinen

Langzeittherapie: keine Indikation zur höherdosierten Langzeitgabe von Neuroleptika

Cave: Spätdyskinesien; pharmakoinduzierte Affektabstumpfung und Leistungsminderung

Phasenprophylaxe: erfolgversprechend wie bei bipolar affektiven Störungen

Rehabilitationsmaßnahmen: stets erfolgversprechend

Psychoses of the psychomotor sphere

Diagnosekriterien für „katatone Schizophrenie“
Internationale Klassifikation psychischer Störungen (ICD-10)

die allgemeinen Kriterien für Schizophrenie (F20) müssen erfüllt sein
(Erstrangsymptome nach K. Schneider)
isolierte katatone Symptome können vorübergehend bei jeder anderen Schizophrenieform vorkommen
klinisches Bild beherrscht von einer oder mehreren der folgenden Verhaltensweisen:

1. Stupor (eindeutige Verminderung der Reaktionen auf die Umgebung sowie Verminderung spontaner Bewegungen und Aktivität) oder Mutismus

2. Erregung (anscheinend sinnlose motorische Aktivität, die nicht durch äußere Reize beeinflußt ist)

3. Haltungsstereotypien (freiwilliges Einnehmen und Beibehalten unsinniger und bizarrer Haltungen)

4. Negativismus (anscheinend unmotivierter Widerstand gegenüber allen Aufforderungen oder Versuchen, bewegt zu werden; oder stattdessen Bewegung in die entgegengesetzte Richtung)

5. Katalepsie (Beibehaltung einer starren Haltung bei Versuchen, bewegt zu werden)

6. Wächserne Biegsamkeit (Verharren der Glieder oder des Körpers in Haltungen, die von außen aufgezwungen sind)

7. Andere Symptome wie Befehlsautomatismus (automatische Befolgung von Anweisungen) und verbale Perseveration

Die Psychomotorik
Bewegungen im psychischen Bereich

Spontanbewegungen → ausdrücklicher Willensimpuls

Reaktivbewegungen

unmittelbare motorische Reaktionen mit <u>flüchtigem Willensimpuls</u> auf äußeren Vorgang oder äußere Eindrücke
(z. B. grüßende, winkende oder andere motorische Zuwendungsreaktionen)

Ausdrucksbewegungen (Expressivbewegungen)

<u>unwillkürliche</u> Bewegungen, die seelische Zustände (v.a. Gefühlszustände) unmittelbar zum Ausdruck bringen (z.B. Mienen, Gesten)

Psychoses of the psychomotor sphere

quantitative disturbances

↓

hyperkinetic-akinetic motility psychosis

qualitative disturbances

“true catatonias”

↓

periodic catatonia

systematic catatonias

Störungen der Psychomotorik I

psychomotorische Hyperkinese

Vermehrung der Reaktiv- und Expressivbewegungen

ausgestaltete → primitivere Bewegungsformen

natürlich ↔ parakinetisch

abwechslungsreich ↔ einförmig

psychomotorische Akinese

Aufhebung von Ausdrucksmotorik, Reaktivbewegungen und Spontanbewegungen

(↔ Antriebsmangel)

reine Akinese ↔ Akinese mit Gegenhalten, isolierten Hyperkinese

Parakinesen

verzerrte, unharmonisch ablaufende Reaktiv- und Expressivbewegungen

Mangel an Flüssigkeit und Abrundung

ruckartige Zwischenbewegungen

steif oder abgehackt wirkende, unvermittelt aussetzende oder einschießende Bewegungen (keine dyskinetischen Zuckungen)
(Expressivmotorik → Grimassieren)

Störungen der Psychomotorik II

Iteration

ständige Wiederholung der gleichen Bewegung (einfach aufgebaut) ohne Ausdruckscharakter oder nachvollziehbaren Sinn

Stereotypie

von Zeit zu Zeit wiederkehrende, einförmig ablaufende Bewegungen

Manieren

verwickelter aufgebaute Bewegungsschablonen, die durch bestimmte äußere Situationen immer wieder ausgelöst werden
feste Gewohnheiten ohne erkennbaren Sinn
in ihrem Ablauf festgefügte und wiederkehrende Handlungsabfolgen (Bewegungsmanieren) oder Handlungsunterlassungen (Unterlassungsmanieren)

psychomotorischer Negativismus

aktives Widerstreben mit charakteristischer Gegentendenz (Ambitendenz), d.h. Schwanken zwischen Wollen und Nichtwollen;
z.B. in der Körperhaltung, im Mienenspiel bei freundlicher Zuwendung seitens Untersucher

Proskinese

abnorme motorische Zuwendungsreaktionen, die auf externe Stimuli hin trotz nachdrücklicher Gegensuggestionen immer wieder auslösbar sind (Anstoßautomatie, Gegengreifen, Mitgehen)

Motility Psychosis

Hyperkinesia:

- pure quantitative increase of motion (independent of disorders of thought or emotion)
- restlessness with increase in expressive and reactive motions
- distractibility by momentary events in the environment with continued senseless motor activity
- incoherent speech, unarticulated screaming

Akinesia:

- disappeareance of reactive motions
- rigid posture and facial expression
- reduction or standstill of voluntary movements (akinetic stupor)
- lack of spontaneous speech
- affective fluctuations, hallucinations

Characteristics of psychomotor disorder in Motility Psychosis

- ***Quantitatively increased or decreased expressive movements***, which appear in connection with mental states.
- ***Quantitatively increased or decreased reactive movements***, which represent immediate reactions to sensory impressions.
- The ***movements usually keep their natural character*** and become only in severe excitation somewhat distorted.

Periodic catatonia

central syndrome
qualitative psychomotor disturbances

hyperkinetic pole

- hyperkinesia with akinetic traits
- psychomotor excitement and restlessness with iterations, stereotypies
- parakinesia, facial grimacing
- distorted movements
- impulsive actions

mixed states

akinetic pole

- akinesia with hyperkinetic traits
- stupor with negativism
- stiff motor activity
- bizarre, stereotype postures
- uniform movements
- perseveration

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intermittent, bipolar course with accessoric hallucinations and delusions

characteristic catatonic residual syndrome with psychomotor weakness of expressive movements, isolated stereotypies, grimacing facial movements, disharmoniously stiff or parakinetic movements and diminished incentive

Die periodische Katatonie

bipolar angelegter, schubförmiger Verlauf mit gewöhnlich akutem Beginn und Remissionen

Residualsyndrom der periodischen Katatonie

- **Reduktion der Ausdrucksmotorik**
- **unharmonische, unmodulierte Reaktiv- und Ausdrucksbewegungen**
- **isolierte Iterationen oder Stereotypien, Hyperkinesen/Akinesen, Grimassieren**
- **Verarmung an Denkinhalten, Kurzschlüssigkeit im Antwortverhalten**
- **Affektabstumpfung**
- **Leistungsinsuffizienz mit psychomotorische Erlahmung bis zu schwerer Antriebsverarmung**

Die periodische Katatonie

therapeutische Prinzipien

hyperkinetische Erregung (in Abhängigkeit von Gereiztheit)
- **hoch- und mittelpotente Antipsychotika**

Akinese mit Negativismus
- **in Abhängigkeit vom Schweregrad des Negativismus**
- **Benzodiazepine und/oder hochpotente Antipsychotika**
- **antriebssteigernde Antidepressiva**
- **Elektrokonvulsionstherapie**

Residualsyndrom der periodischen Katatonie
- **cave: Verstärkung der psychomotorischen Adynamie**
- **antriebssteigernde Antidepressiva**
- **Clozapin oder Antipsychotika der 2. Generation**
- **Dosisreduktion**

Affektschwankungen: syndromaler Therapieansatz

anxiety-happiness psychosis vs affectladen paraphrenia

The onset and the early course of schizophrenia

subjektives Wahrnehmen der Erkrankung im Beginn:
non-spezific aczessoric symptoms („Epiphenomina“)

I. Veränderungsideen:

Veränderung wird auf Umwelt bezogen => Hypnosegefühl, Gefühl, daß Außergewöhnliches geschieht
Katastrophen-/Weltuntergangserlebnisse mit Ängstlichkeit und Ratlosigkeit

II. flüchtige Beziehungs- und Bedeutungsideen:

Vorgänge der Umgebung können nicht mehr richtig eingeordnet und verarbeitet werden (“Wahnstimmung, primäre Wahnerlebnisse”)

Wahn und Wahnideen
Störungen des Gedankeninhaltes

- formale Denkstörung erzeugt falsche Denkinhalte, die aber nicht festgehalten werden (keine echten Wahnideen)

- durch *Hinzutreten eines Gefühlsvorganges* wird der krankhafte Inhalt fixiert ==> Wahnideen, paranoide Ideen

Meinungen - überwertige Ideen - abnorme Überzeugungen

gefühlsnahe Ideen:
Ideen der Selbsterhöhung: Größenideen
Ideen der Selbsterniedrigung: Kleinheitsideen
Beeinträchtigungs- und Verfolgungsideen: Eigenbeziehungen (Beziehungsideen)
hypochondrische Ideen

absurden Ideen: Hinzutreten einer logischen Denkstörung (Störung der logischen Gedankenverbindung)

Anxiety-Happiness Psychosis

Anxiety:

- severe anxiety with distrust and ideas of reference
- ideas of threat or persecution
- anxiety with paranoid features or mood congruent sensory illusions or hallucinations (e. g. threatening voices)
- anxiety with hypochondriacal somatic sensations

Ecstacy:

- ecstatic mood and feelings of happiness with illusonary and hallucinatory experiences
- ecstatic ideas with altruistic components (religious ideas, social/ political tasks)
- affective waves with ideas of being called, elevated to a devine level or inspired by God

Ideenbildungen und Wahnideen

schizophrene Psychosen im Beginn:

Veränderungs-, Beziehungs- und Bedeutungsideen

=> unspezifische, vorübergehende Ideen

(„Wahnstimmung“, „abnorme Eigenbeziehungssetzungen“, „primäre Wahnerlebnisse“)

Wahn im eigentlichen Sinn:

<u>überdauernde</u> Störung des Gedankeninhaltes
fehlerhafte, unlogische Beziehungssetzung ohne Anlaß
Verdrehung und Fehlerhaftigkeit im Urteil
mit subjektiver Gewißheit und Unkorrigierbarkeit

Affect-laden Paraphrenia

Historical overview:
- Paranoia bzw. Paraphrenia systematica (Kraepelin)
- importance of the pathological affect in paranoia (Specht)
- progressive Beziehungspsychose (Kleist)

Core symptoms:
ideas of reference closely linked to affective irritation and affective fluctuations associated with irritability

initial stages:
delusions and hallucinations grow out of anxiety or ecstacy

episodic-remitting or continuous course:
ideas no longer deduced by anxiety/ecstacy
=> hostile mis-interpretations of the environment

Affect-laden Paraphrenia

Core syndrome:

- irritated reference syndrome („Beziehungssyndrom“)

- anxiety with self-reference and hallucinations

- ecstacy with false perceptions („love delirium“)

both accompanied by progressive illogical thinking

- ideas no longer deduced by anxious or ecstatic mood, but strongly anchored in a over-sensitive affectivity

- acustic hallucinations

- somatic hallucinations and misperceptions with the feeling of being influenced from outside

- delusions of persecution („Persekutivparanoia“)

- delusions of immense grandeur („Expansivparanoia“)

Affect-laden Paraphrenia II

episodic-remitting with residual symptoms or continuous course

- hostile reinterpretations of the environment
- systematization of the delusions (absurd, fantastic ideas) with maintained dominant affective display
- errors of memory (confabulations), misidentifications
- speak about their ideas of reference or grandeur with deep irritation or with pride and enthusiasm

- secondary to the affectively anchored delusions:
  blunted affectivity
  loss of incentive
  loss of interests
  overly sensitive, often denying delusional symptoms

Störungen des Affekts bei schizophrenen Psychosen

eine ***einheitliche*** „schizophrene Affektstörung“ ***gibt es nicht***.

(„Die schizophrenen Gefühlsstörungen lassen sich kaum beschreiben.“ Wieck 1967)

verschiedene diagnostisch richtungsweisende Störungsformen

- „quantitativ“: Verschiebung zur Lustseite oder Unlustseite
- „qualitativ“: Abstumpfung / Verflachung höherer seelischer Gefühle

paranoischer Affekt: Wahnideen behalten tiefe affektive Bindung, auch wenn sie phantastische Züge annehmen

systematische Paraphrenien: Affekt entspricht meist nicht den Wahnideen, Gleichmut bei Berichten über absurde oder expansive Ideen

Hebephrenien: Affektverflachung ist zentrales Syndrom mit spezifischen Ausfällen in den Unterformen

confusion psychosis vs cataphasia

Störungen des formalen Denkens und der Sprache bei schizophrenen Psychosen

- eine ***einheitliche*** „schizophrenen Denkstörung“ ***gibt es nicht***.

- ***verschiedene diagnostisch richtungsweisende Störungsformen des formalen Denkens***.

- ***Kardinalsymptome sind*** formale Denkstörungen bei

  - erregt-gehemmter ***Verwirrtheitspsychose*** (zykloide Psychose),

  - Kataphasie (unsystematische Schizophrenie),

  - systematischen Paraphrenien .

Störungen des Denkens bei schizophrenen Psychosen

Unterscheidung zweier verschiedener Arten von Denkstörungen (erstmals bei Griesinger):

- formale Denkstörungen: Störungen der Gedankenverbindung (Gedankengang bzw. Gedankenordnung)
- inhaltliche Denkstörungen: Störungen der Gedankeninhalte bzw. der Themen des Gedankenganges.

Klinische Prüfung des formalen Denkens und der sprachlichen Ordnung

- Beurteilung von Ablauf (Tempo, Flüssigkeit) und logischer bzw. thematischer Ordnung der freien Rede
- Beurteilung von Begriffsbildung, Begriffshandhabung und grammatischer Ordnung der Äußerungen
- Bei Verdacht auf Vorliegen formaler Denkstörungen immer zusätzlich Denkprüfung mittels standardisierter Vorgaben, die zu abstrakten Gedankengängen anregen sollen.
  - Begriffsunterscheidungen,
  - Sprichwortinterpretationen,
  - Begriffe erklären,
  - Satzbildung aus 3 vorgegebenen Worten,
  - Fabel nacherzählen,
  - Bilder erklären.

Confusion Psychosis

Excitation:

- incoherence of thought process (incoherence of thematic choice) with pressure of speech
- disgressive choice of theme
- ideas of significance or reference
- fleeting misidentifications of persons or hallucinations
- rapid affective fluctuations

Inhibition:

- inhibition of thought process with verbal impoverishment
- perplexity and mutism
- ideas of significance or reference
- acustic or somatopsychic hallucinations

Characteristics of formal thought disorder in Confusion Psychosis

- ***Incoherence of thematic choice***: lack of comprehensible logical or associative connection between individual themes whereas within an actually chosen theme there are no logical semantical or syntactical faults.

- ***Digressive choice of theme*** (in less severe cases): the logical connection of the themes is not totally abandoned, but single concepts of one theme determine the content of the following theme. In contrast to the digressive flight of ideas of manic patients each thought is held on to for a while.

Cataphasia (Schizophasia)

subtype of the unsystematic schizophrenias

central syndrome: qualitative thought disorder

exhibited pole

- confused pressure of speech
- logical blunders and derailments
- wrong choice of words, neologisms, contaminations. „Wortsalat“
- confabulations
- uniformity of verbal expression
- grammatical and semantic errors, paragrammatism

inhibited pole

- thought inhibition with poverty of speech or mutism with logical errors, syntactic and semantic errors
- ideas of reference
- numbing of reactivity, and facial expression
- blunted staring at the examiner

intermittent, bipolar course with ecstatic mood fluctuations
accessoric hallucinations and delusions
behaviour remain sensible, activities preserved with blunted, indifferent affectivity
persistent logical errors, paralogic thinking (proverbs)

Inkohärenz

Nebeneinandertreten beziehungsloser Denkinhalte,

nicht logisch ausgeformt im Sinne eines festgehaltenen und logisch bearbeiteten Themas.
Übergeordneter "roter Faden" ist nicht mehr erkennbar
keine regelrechten assoziativen Brücken zwischen den Einzelbegriffen und Gedanken (<=> assoziative Lockerung)

Logische Entgleisung

Auftreten logisch widersprüchlicher Gedanken- und Begriffsverbindungen, v.a. bei freier Rede ohne konkrete Führung durch unmittelbare Anknüpfungspunkte (bereitliegende Themen, vorgegebenes Antwortverhalten).

Störungen der grammatischen Ordnung

Wortverwechslungen und logisch unsinnige Wortneubildungen

Disorder of thought and language in cataphasia

An incoherence of thought is combined with logical derailments and paralogias: there are severe logical blunders in the organization of concepts and ideas which in severe cases may lead to a completely incomprehensible word salad.

Disorder of speech with semantic mistakes, neologisms, paragrammatism.

In the inhibited form the thought disorder often is more difficult to judge due to the poverty of speech up to mutism; then perplexedness with numbing of expression and reactivity indicates the thought disorder.

Despite the severe thought disorder usually relatively appropriate activity in day to day life.

The biological basis of the cycloid psychoses

Proband-wise concordance rates in same-sex twins with schizophrenic psychoses

47 monozygotic and dizygotic pairs (Upper Franconia) with at least one of the twins hospitalized for schizophrenia spectrum disorder (Beckmann & Franzek, 1999)

	Monozygous Twins	Dizygous Twins	Index of hereditariness
Systematic schizophrenias			
number of index cases	0	6	-
concordant twins	-	0 (0%)	
Unsystematic schizophrenias			
number of index cases	18	8	0,72
concordant twins	16 (89%)	2 (27%)	
Cycloid Psychoses			
number of index cases	13	13	0,21
concordant twins	5 (39%)	4 (31%)	

Cycloid Psychosis in Twins

Systematic twin study on 47 monozygotic and dizygotic pairs (Upper Franconia) with at least one of the twins hospitalized for schizophrenia spectrum disorder (Franzek and Beckmann 1999)

Diagnosis of cycloid psychosis: 13 twin index-cases
11 monozygotic and 11 dizygotic pairs

concordance rate (probandwise):	monozygotic twins (n=5)	39 %
	dizygotic twins (n=4)	31 %

heretability-index: 0,21
MZ/DZ-Quotient: 1,25

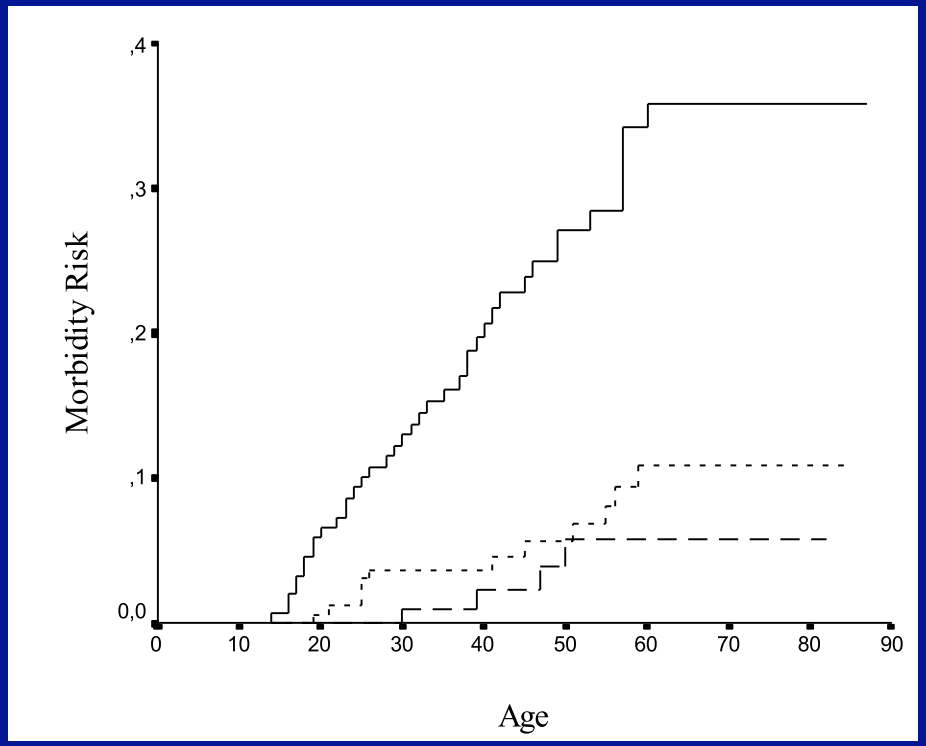
→ hereditary factors play a minor role in cycloid psychoses

Cycloid Psychosis: a controlled family study

	Cycloid Psychosis (n=45)	MDI (n=32)	Controls (n=27)
N relatives ≥ 18 years of age	172	153	106
N living relatives	157	133	93
mean age (years)	48,5	47,2	50,0
N personally examined relatives	146	123	84
mean age (years)	48,8	47,4	49,9

Cycloid psychoses

morbidity risk of first degree relatives for endogenous psychoses



35.2 %

p < 0.05

10.8 %

5.7 %

n. s.

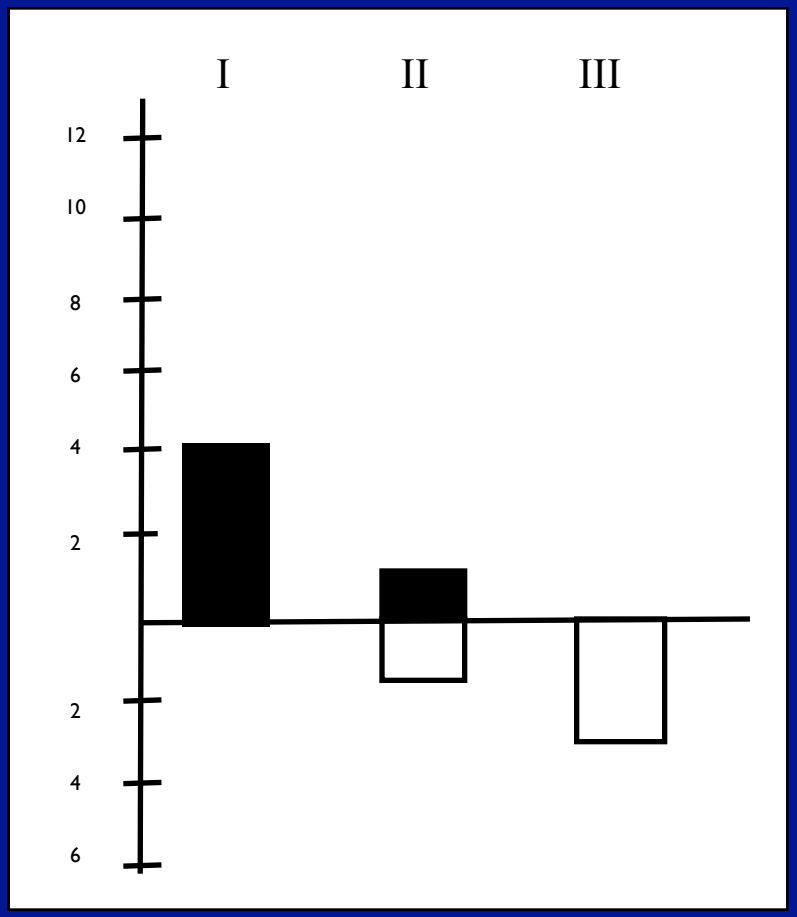
———— manic-depressive illness (32 index cases; 153 first degree relatives)
- - - - - - - - cycloid psychosis (45 index cases; 172 first degree relatives)
— — — — controls (27 index cases; 106 first degree relatives)

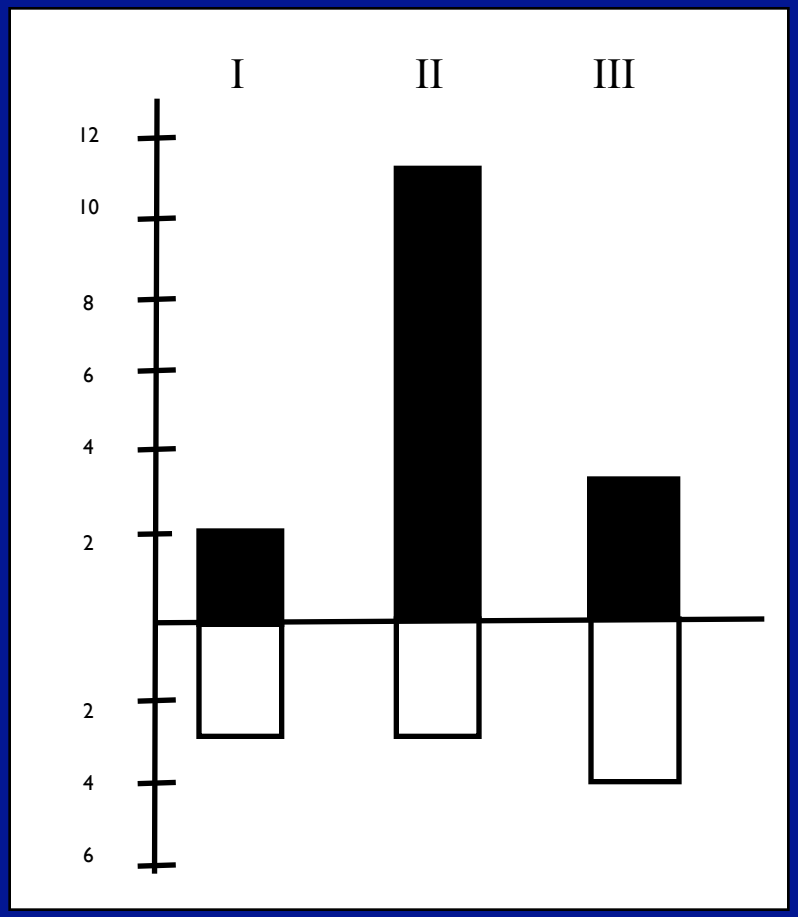
Exposure to prenatal infections in individuals with cycloid psychosis and

cycloid psychosis (n = 40)

chronic schizophrenia (n = 80)

Individuals exposed to prenatal respiratory infections





controls and bipolar disorder (n = 80)

controls (n = 40)

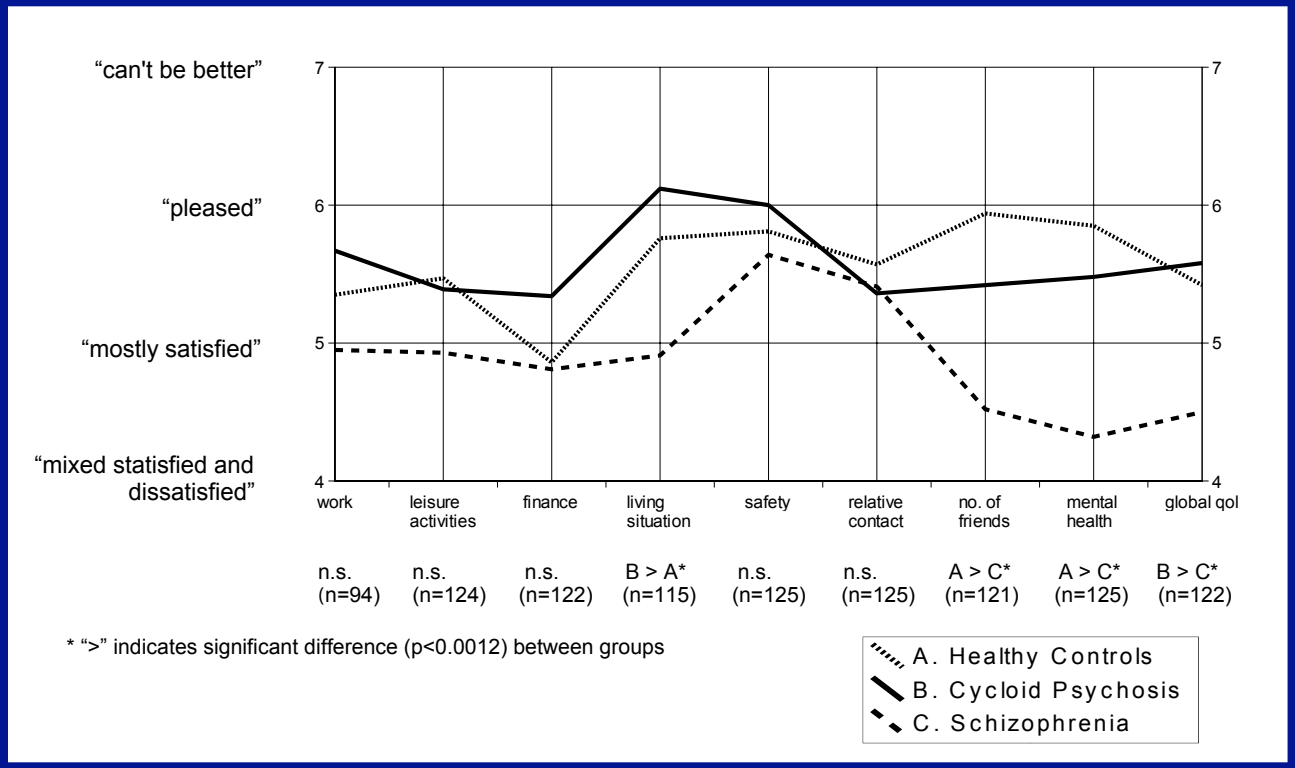
Stöber et al.1992, 1994, 1997

Minor physical anomalies across diagnostic subgroups

minor physical anomalies (items: n=129)	all cases	males	females	affective psychoses	cycloid psychoses	unsystematic schizophrenia	systematic schizophrenia
	130	90	40	30	38	37	25
head shape (n= 8)	+	+	-	-	+	-	-
hair (n= 6)	+	+	-	-	+	+	-
nose (n= 9)	+	+	+	+	-	+	-
chin (n= 4)	-	-	-	-	-	-	-
eyes (n= 17)	+	+	-	-	-	-	-
mouth (n= 13)	+	+	+	-	+	+	-
ears (n= 14)	-	-	-	-	-	-	-
skin (n= 10)	-	-	-	-	-	-	-
spine (n= 1)	-	-	-	-	-	-	-
limbs (n= 6)	-	-	-	-	-	-	-
hands (n= 18)	-	-	-	-	-	+	-
feet (n= 15)	+	-	-	-	-	-	-
hernia (n= 3)	-	-	-	-	-	-	-
others (n= 5)	-	-	-	-	-	-	-

Stöber & Hanewinkel, in preparation

Quality of life: individual statements



Jabs et al., 2004

Cycloid Psychoses and postpartal manifestation

Follow-up study (at an average of 12.2 years) in 39 systematically assessed female in-patients with severe postpartum psychiatric disorders (Pfuhlmann et al., 1998):

Cycloid psychosis	54 %
Manic-depressive illness	13 %
Unsystematic schizophrenias	10 %
Unipolar depression	8 %
Reactive depression	10 %
Exogenic psychosis	3 %

→ Cycloid psychoses account for the majority of severe postpartum psychiatric disorders with excellent outcome of SCOS 14.8 (±)

Cycloid Psychosis

results of an on-going prospective 10-years follow-up study:

Sample collection: consecutive assessment of all in-patients of an open ward at the Department of Psychiatry and Psychotherapy, University of Würzburg, Germany

period of recruitment: April 1991- March 1992
with a total of 220 index cases
all index cases were diagnosed according to differentiated psychopathology in personal examinations in a clinical assessment

Re-evaluation starting in June 2002:

independent and personal re-examination of all index cases born after 1945 who were initially diagnosed as suffering from cycloid psychosis or manic-depression without knowledge of the initial diagnosis
(in most cases at the proband's resident)

Cycloid psychosis and manic-depression: a prospective 10-years follow-up

	Diagnosis in 1991/92				
	total	females	males	manic-depression	cycloid psychosis
probands n (%)	88 (100%)	54 (61%)	34 (39%)	43 (49%)	45 (51%)
reinvestigated as of 10/2004	35 (40%)	19 (54%)	16 (46%)	19 (54%)	16 (46%)
deceased	5 (6%)	2 (2%)	3 (3%)	2 (2%)	3 (3%)
unknown	1 (1%)	-	1 (1%)	-	1 (1%)

Cycloid psychosis and manic-depression: a prospective 10-years follow-up

Diagnosis in 1991/92

total sample			manic-depression		cycloid psychosis	
total	females	males	females	males	females	males
35	19 (54%)	16 (46%)	10 (53%)	9 (47%)	9 (56%)	7 (44%)

Re-evaluation in 2002/04

	manic-depression		cycloid psychosis	
	females	males	females	males
	10 (53%)	8 (42%)	9 (56%)	4 (25%)
periodic catatonia	-	1 (5%)	-	2 (13%)
affectladen paraphrenia	-	-	-	1 (6%)

Cycloid psychosis and manic-depression: a prospective 10-years follow-up soziodemographic data of the initial sample in 1991/92

	manic-depression			cycloid psychosis			
	total	females	males	total	females	males	p-value
probands	43	27 (63%)	16 (37%)	45	27 (60%)	18 (40%)	ns
age at first-hospitalization (years)	27.6	29.3	24.7	25.4	25.3	25.4	ns
age at index episode (years)	30.1	31.8	27.2	30.0	30.3	29.4	ns

Cycloid psychosis and manic-depression
a prospective 10-years follow-up study

Clinical data of the re-evaluated sample

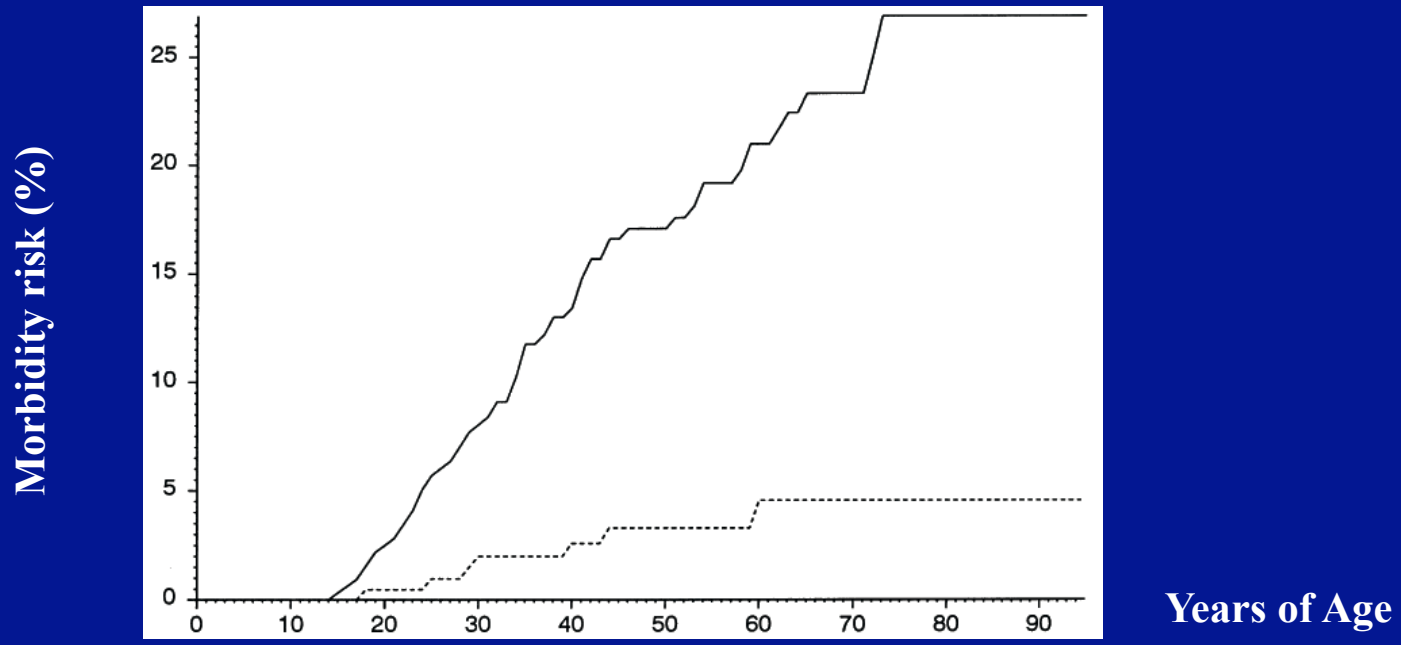
	Manic-depression (n= 18)	Cycloid psychosis (n= 13)	P-value
Age at first hospitalization (years)	28.0 (SD 7.7)	25.8 (SD 7.6)	0.42
Age at index episode (years)	29.9 (SD 8.4)	31.8 (SD 6.7)	0.49
Age at re-evaluation (years)	41.9 (SD 8.3)	44.1 (SD 6.9)	0.42
Clinical Global Impression Scale	2.9 (SD 1.2)	3.5 (SD 1.1)	0.15
Global Assessment of Function Scale	76.3 (SD 10.6)	71.6 (SD 12.2)	0.29
Strauss-Carpenter Outcome Scale	14.6 (SD 1.7)	13.5 (SD 2.2)	0.11

The unsystematic schizophrenias: cataphasia and periodic catatonia

Genetic-epidemiologic and biological findings

Morbidity Risk of First Degree Relatives

Periodic Catatonia vs Systematic Catatonias

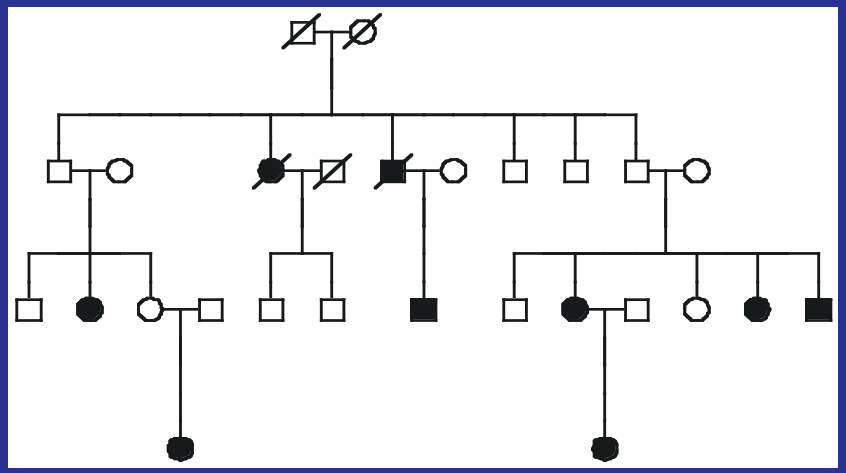


Periodic catatonia (83 cases; 323 first degree relatives)

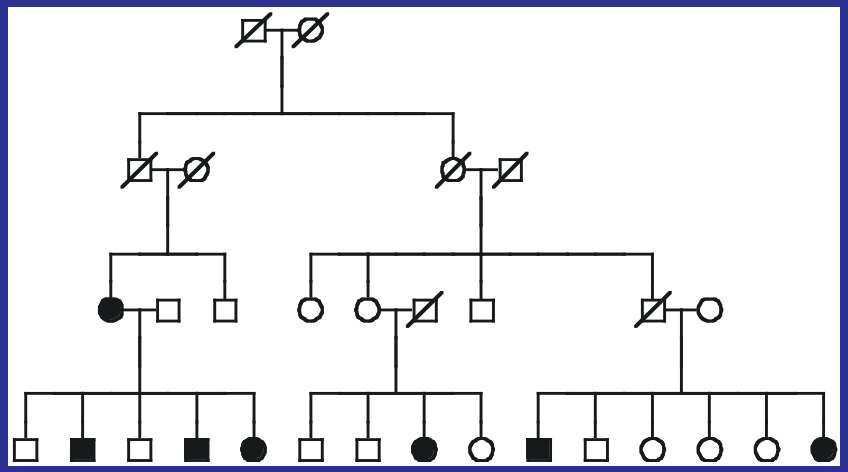
Systematic catatonia (56 cases; 220 first degree relatives)

Familienkollektiv für genomweite Kopplungsstudie bei periodischer Katatonie

Pedigree 11

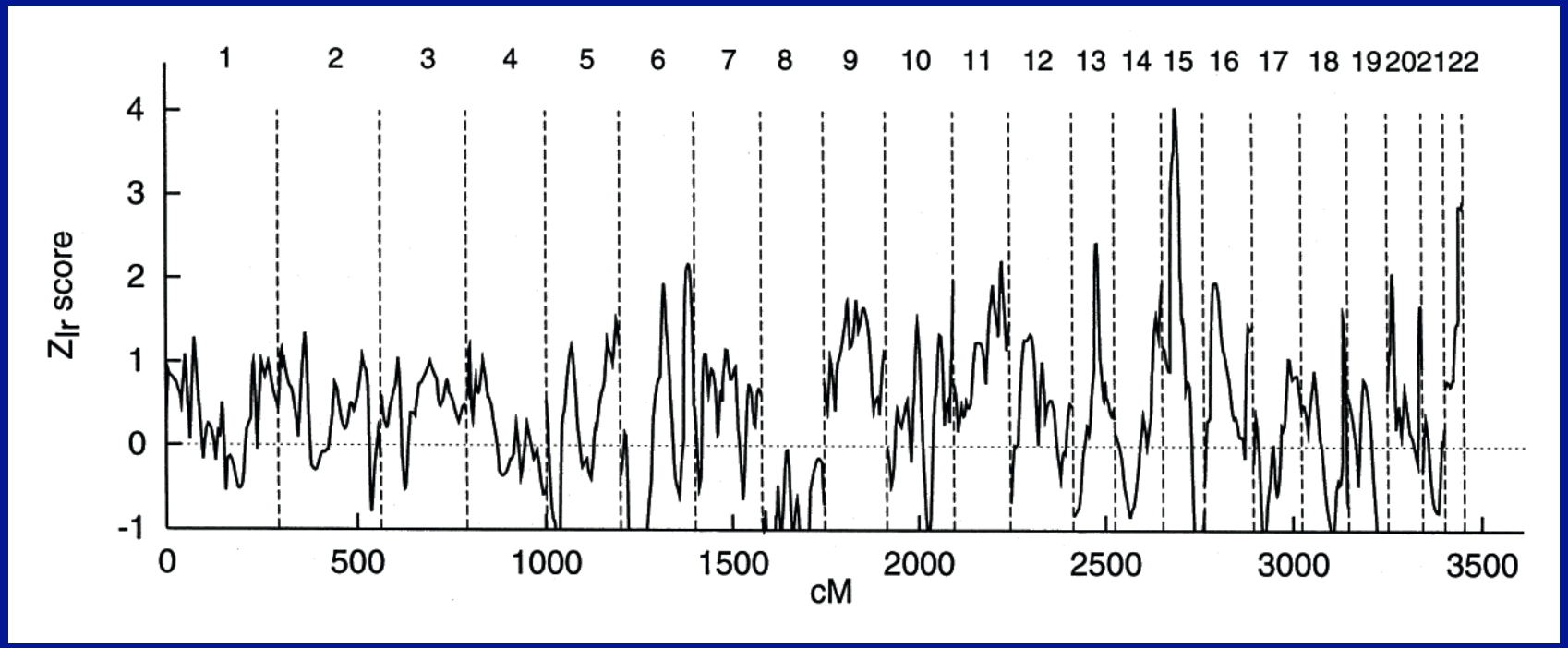


Pedigree 21



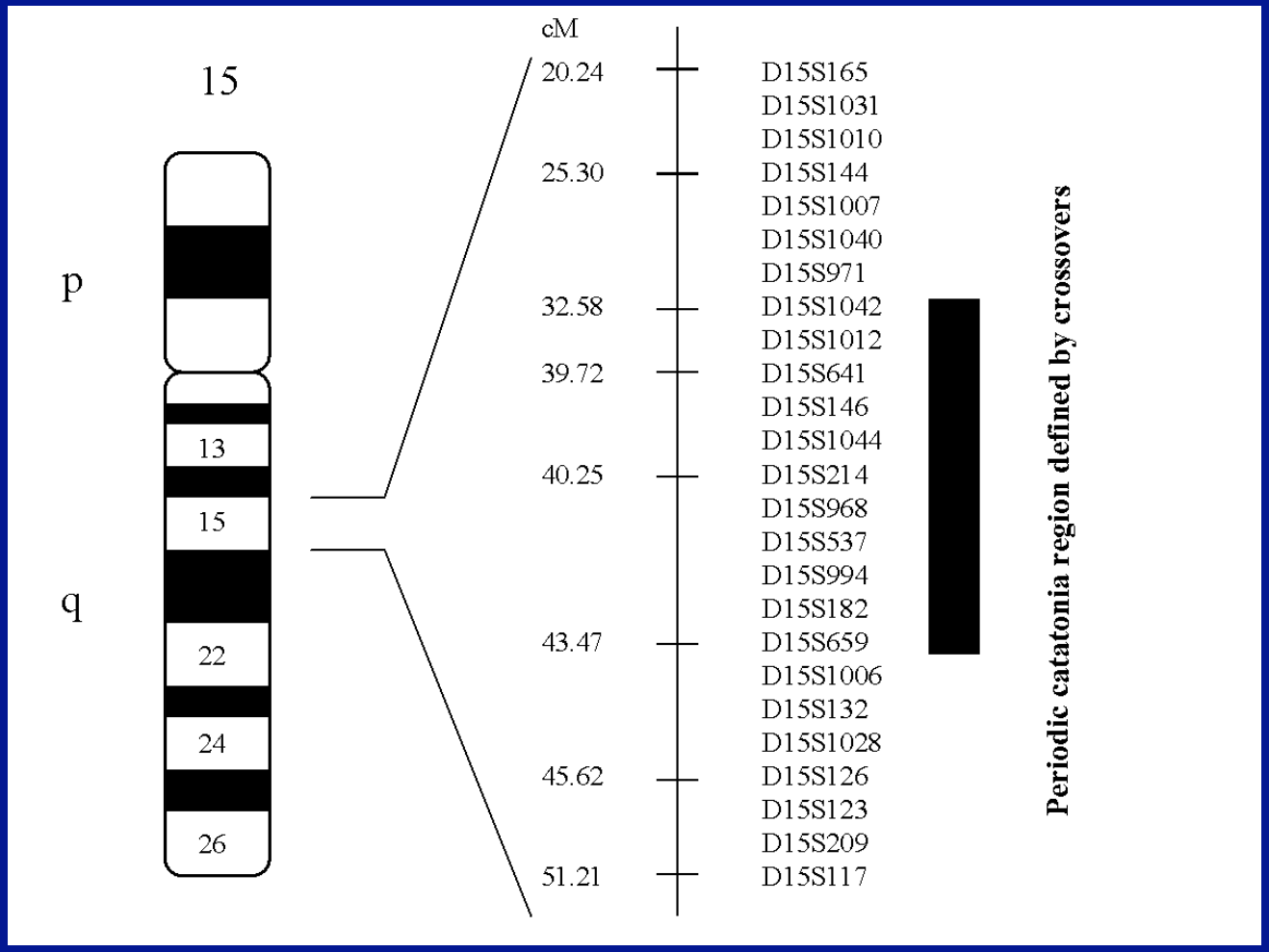
Genomewide Linkage Scan I in Periodic Catatonia (12 Pedigrees)

Non-parametric multipoint analysis (Genehunter-Plus)

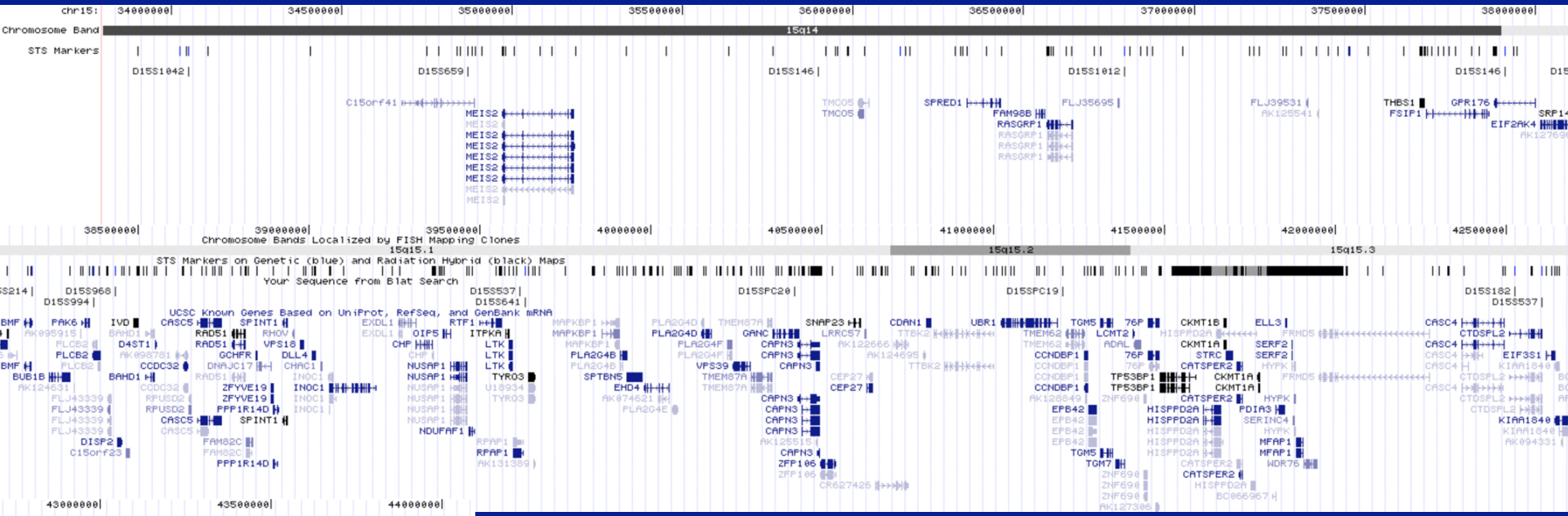


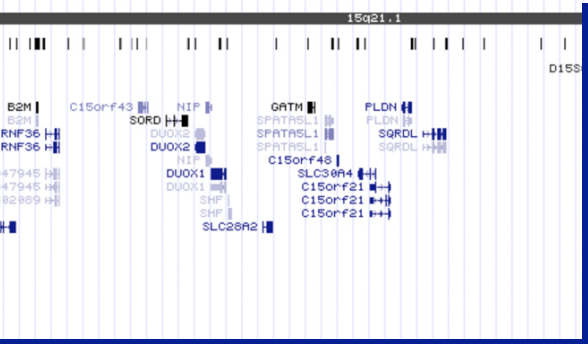
Stöber et al. Am J Hum Genet 2000

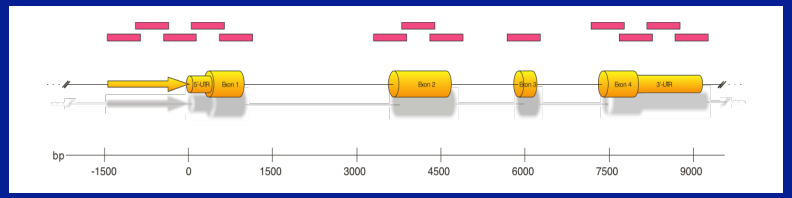
Periodic catatonia:
Major Gene Locus on Chromosome 15q15



Positional cloning approach - systematic mutation screening







Gene	Potential Function	Position (Mb)	Number of SNPs
Meis2	hox-DNA binding cofactor (mouse) homolog 2	30079195 - 30286139	2
KIAA0945	large brain expressed protein of unknown function	33627659 - 33656167	3
KIAA0252	large brain expressed protein of unknown function	34605175 - 34671002	10
KIAA1403	large brain expressed protein of unknown function	34705197 - 34732287	23
Tyro 3	receptor protein tyrosine kinase	34747219 - 34767358	7
β-spectrin V	beta V spectrin	35036168 - 35082098	51
EHD4	EH-domain containing protein	35087461 - 35160567	12
SNAP 23	synaptosomal- associated protein	35683658 - 35721079	6

Periodic catatonia: analysis of samples

	K. Leonhard, 1999			Stöber et al.			total sample		
Period of assessment	before 1985 reassessment 2002-2006			1991-1992 10/1995-12/2007					
Sample	total	males	females	total	males	females	total	males	females
Index cases	90	43	47	242	136	106	332	179	153
Age at first hospitalization	21.4 ±7.0	23.0 ±5.8	26.5 ±7.9	25.5 ±10.1	24.1 ±9.4	27.1 ±10.6	24.5 ±9.6	23.2 ±8.8	25.9 ±10.3

(years ± standard deviation)

Genomewide single-nucleotide-polymorphism association study

Phase I SNP microarray and DNA pooling study (SNP-MaP)
allelotyping of pooled genomic DNA, ranking of SNPs

Phase II replication and reranking of alleles
in case-control sub-pools

Phase III individual genotyping of SNPs in associated loci

Phase IV additional validation in new cohorts and
fine-mapping haplotypes

Phase V systematic mutation screening of associated haplotypes

Phase I: Pooling-based genomewide SNP association study

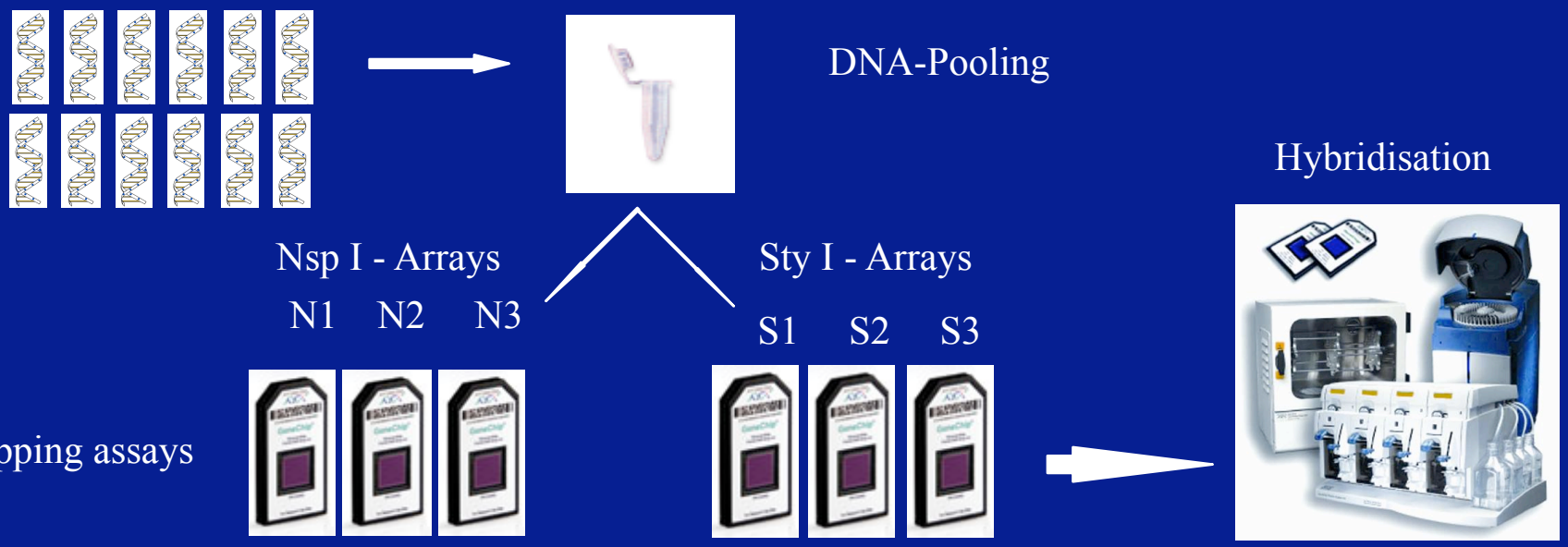
Affymetrix: GeneChip® 500K - SNP-Array

500k Chip – 500.568 SNPs

incl. 1242 SNPs at chromosome 15q15

pooling of DNAs (checking probe intensity and quantifying DNA, placed into subpools)

triplicate technical replicates (total of 30 arrays)



Samples for microarrays and DNA pooling

splitting the samples in different pools for replication analysis

past quality check:

P1 - 84 index cases (incl. cases of Chr. 15q15-linked or possibly linked pedigrees)

P2 - 84 index cases

P3 - 77 index cases from Leonhard‘s study

P4 - 108 controls

P5 - 108 controls

Analysis tools

GenePool software package (genepool.tgen.org/)

GPextract

GPanalysis: Pooling-based allelotyping

raw data transformation of probe intensity data and normalisation

detection of shifts in relative allele frequency (RAF)

„GPGraphics“ tool (S. Uebe, Erlangen) for visualisation and graphic presentation of RAF-shifts

Initial experiments: Cystic fibrosis

cystic fibrosis transmembrane conductance regulator (CFTR)
gene map locus 7q31.2, 1480 amino acids
24 exons spanning 250kb, extensive allelic heterogeneity

Cystic fibrosis DNA-Pool (n= 96)

75% ΔF508

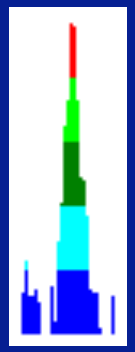
shifts in relative allele frequency (RAF)

ranking by t-test statistics

cut-off 20, log-rank filter $e^{1,00}$

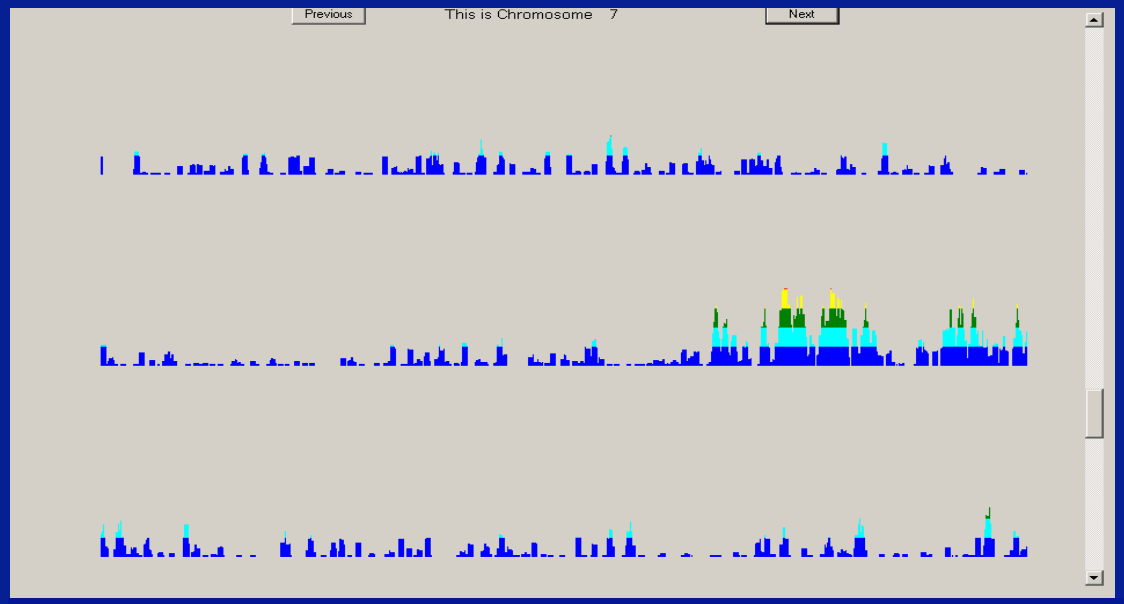
sliding window = 5

ranking order



+++++	Class 1
++++	Class 2
+++	Class 3
++	Class 4
+	Class 5

GPGraphics: Chr. 7



Phase I & II: Pooling-based genomewide association study in periodic catatonia

P1 vs controls (P4) <u>and</u> P2 vs controls (P5)

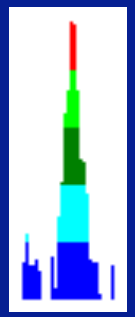
statistical SNP ranking → 205 markers appear in both subpools

24 marker class 1-3

2x class 1 (1-1 / 1-3)

12x class 2 (2-2 / 2-3)

10x class 3 (3-3)



P3 (Leonhard's index cases) vs controls (P4/P5)

replication of 10 marker peaks with level class ≥4

- analysis of 3 sub-pools

SNPs at chromosomes 4, 5, 7, 10, and 19

with replicated ranking at the top class of markers across all sub-pools

Phase III High-density SNP genotyping

Genomewide pooling-based association study: estimated allelotyping ratios

permutation test (10.000 replicates) using Haploview 4.0

SNP-Nr.	Chromosome	Associated Allele	Cases	Controls	Chi Square	p-value
1	4	T	0.460	0.424	1.822	0.1771
2		T	0.677	0.593	10.979	*0.0009*
3		G	0.654	0.585	7.047	0.0079
4	5	T	0.608	0.564	2.806	0.0939
5		G	0.629	0.571	4.979	0.0257
6		A	0.627	0.572	4.418	0.0356
7	7	A	0.699	0.605	13.148	*0.0003*
8		G	0.782	0.730	5.13	0.0235
9		A	0.588	0.559	1.15	0.2835
10		T	0.589	0.540	3.359	0.0668
11	10	C	0.901	0.883	1.185	0.2762
12		G	0.799	0.775	1.144	0.2848
13	19	G	0.894	0.853	5.232	0.0222
14		A	0.881	0.840	4.753	0.0292
15		G	0.753	0.659	14.747	*0.0001*

Genotyping of SNPs in associated loci

TaqMan assays: 294 index cases with PECA vs 455 controls
permutation test (10.000 replicates) using Haploview 4.0

SNP Nr.	Chromosome	Associated Allele	Cases	Controls	Chi Square	p-value
1	4	T	0.462	0.423	2.107	0.1466
2		T	0.679	0.591	11.779	*0.0006*
3		G	0.654	0.585	7.047	0.0079
4	5	T	0.608	0.563	2.969	0.0849
5		G	0.627	0.571	4.687	0.0304
6		A	0.625	0.572	4.172	0.0411
7	7	A	0.701	0.605	13.659	*0.0002*
8		G	0.782	0.729	5.23	0.0222
9		A	0.586	0.559	1.011	0.3147
10		T	0.585	0.540	2.896	0.0888
11	10	C	0.899	0.883	0.963	0.3264
12		G	0.799	0.776	1.098	0.2947
13	19	G	0.893	0.853	4.78	0.0288
14		A	0.879	0.840	4.345	0.0371
15		G	0.752	0.658	14.304	*0.0002*

Ongoing studies and future directions

Phase IV additional validation in new cohorts and fine-mapping haplotypes

a. further replication cohorts

340 index cases with periodic catatonia vs

1100 index cases of other subgroups of the endogenous psychoses

b. external replication samples

1000 cases with „schizophrenia“

500 cases with unipolar/bipolar affective disorder

Phase V systematic mutation screening of associated haplotypes

Phase VI copy number variants (CNV) for chromosomal deletions and duplications

Kraepelin's Schizophasia (1913; 8th ed.)

- Insidious beginning, chronic course with relapses and partial remissions
- Initially, decline of interest and social functioning, followed by delusions and hallucinations
- Poor outcome similar to "dementia praecox"
- Main feature: pronounced formal thought disorder with pressure of speech, incoherence and neologisms
- No disorganized behaviour in every day life

Formal thought disorder
Hebephrenia: ICD-10 vs Leonhard

ICD-10

Meets general criteria for schizophrenia

Disorganized thought, speech and behaviour

Flat and inappropriate affect

Leonhard

Distinct clinical entities with clear-cut symptom constellations

Main feature: Specific disturbance in affectivity and initiative

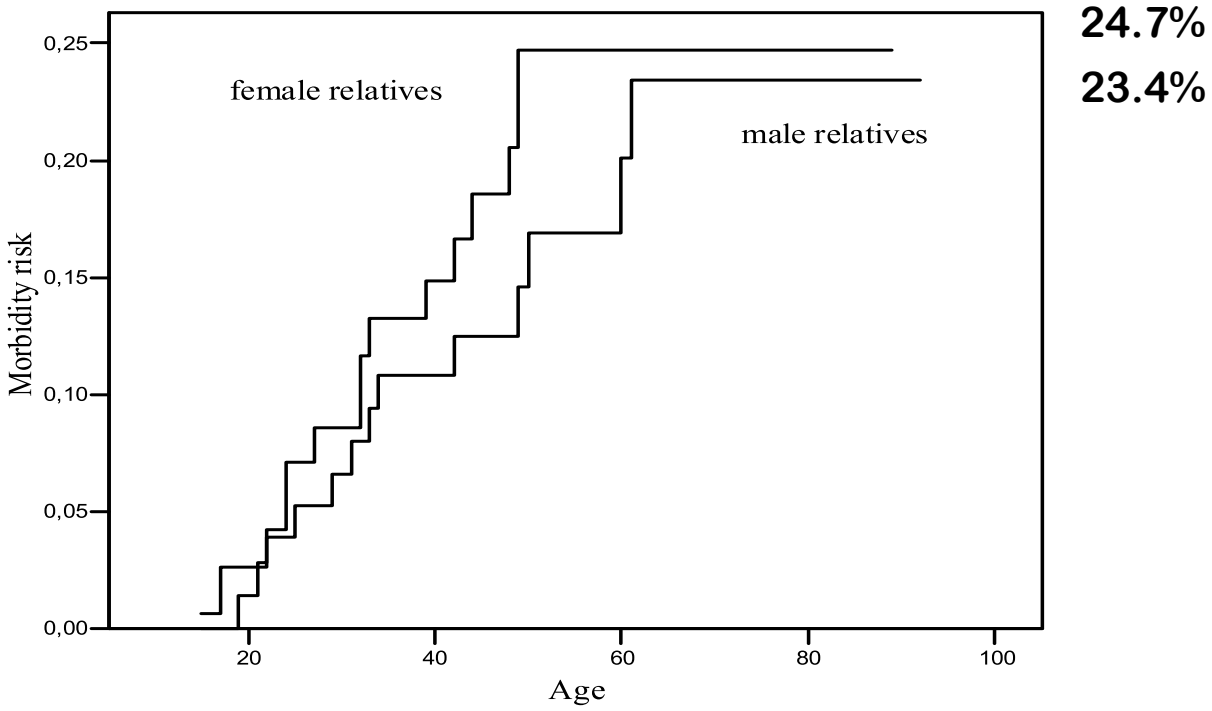
insufficient, but no paralogic thought process

Family Study on Cataphasia
31 Index cases: sociobiographical and clinical data

m/f	25/ 6
Age at study (y)	43.6 (20-69)
Married/ cohabitating (%)	32.3
Occupation 1st market(%)	19.4
Age at first treatment (y)	24.7 (15-55)
No. of illness episodes	8.8 (1-26)
- excited/ inhibited/ unspecific (%)	35/ 43/ 22
Life time hospitalisation (wk)	116 (4-749)
CGI	4.8 (3-8)
GAF	50.2 (11-75)
PANSS	51.3 (34-101)

Cataphasia - Family Study

Morbidity risks of 24.0% among first degree relatives (n= 148) for endogenous psychoses in 31 index cases

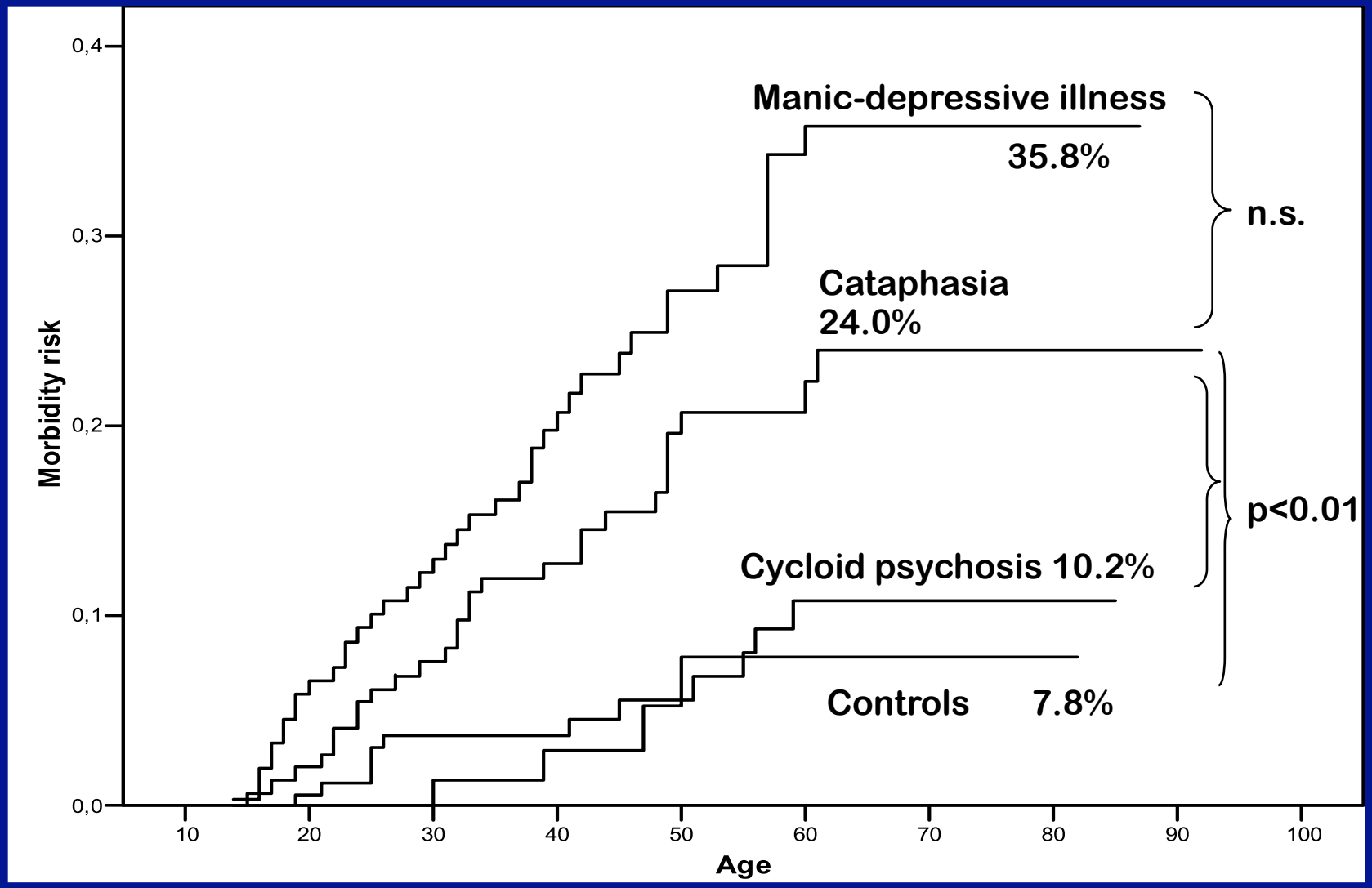


24.7%

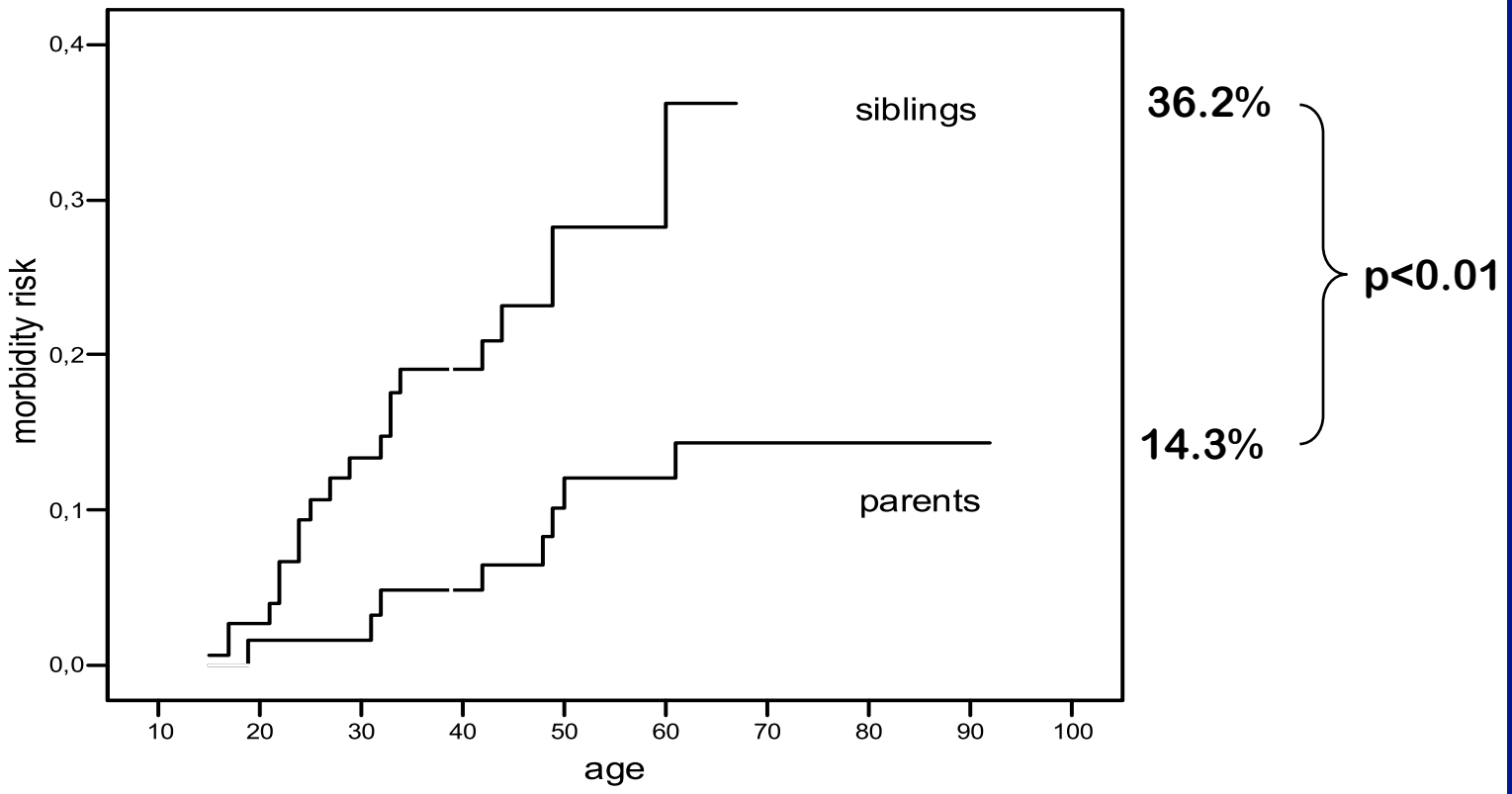
23.4%

Family Study on Cataphasia

Morbidity risks in different nosological entities



Family Study on Cataphasia
Morbidity risks in parents and siblings



Family Study on Cataphasia - Conclusions

- High genetic loading, comparable to manic-depressive illness
- High rate of homotypical cases in first degree relatives (75% of cases with endogenous psychoses)
- No cross-prevalence with manic-depressive illness despite its bipolar character
- No support for a schizo-affective spectrum
- Cataphasia seems to be a genetically independent nosological entity, thus deserving further molecular genetic research

A proposal for a nosological classification of the endogenous psychoses

Distinct phenotypes with different aetiology according to differentiated psychopathology

***Cycloid psychoses*:** **low genetic loading according to family and twin studies**
early noxious events (first trimester gestational infections; MPAs)

***Systematic schizophrenias*:** **low genetic loading according to family and twin studies**
early noxious events (second trimester gestational infections)

***Unsystematic schizophrenias*:** **valid phenotypes in the schizophrenic spectrum**

periodic catatonia: genetically mapped to chromosome 15q15, and genetic heterogeneity

cataphasia: major gene effect with morbidity risk of 24% among first degree relatives