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ORIGINAL PAPER

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The predictive validity of the Leonhardean classification of endogenous psychoses

A 21-33-year follow-up of a prospective study ("BUDAPEST 2000")

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Abstract To our knowledge, no previous long-term studies of the Leonhardean classification in the whole spectrum of endogenous psychoses have been conducted. This prospective study (n = 276; female patients n = 222; normal control persons n = 54) started in 1967–1976. The same population was followed-up by participation of a "blinded control" psychiatrist in 1997–2002 [patients available at follow-up = 125 (56.3%); available controls = 38 (70.4%)]. Patients for this investigation were selected by two independent diagnosticians from eight nosological groups based on full diagnostic agreement. Diagnostic agreement at follow-up (weighted-kappa) was 0.87. Predictive validity of the diagnostic categories was measured empirically and using a stochastic (Markovian) model, thus combining validity and reliability. Hebephrenias, group of normal persons and of schizophrenias proved to be valid categories, with diagnostic stabilities of 0.94, 0.91, and 0.93, for the three groups, respectively. In addition, bipolar manic-depressive psychoses and cycloid psychoses were also valid (diagnostic stability of 0.77 and 0.76, respectively). Unipolar depression was valid (diagnostic stability = 0.84) only by forming a "nosological family" based on diagnostic stability and on current status and clinical presentation during the period preceding the follow-up with regard to other mood-congruent disorders and outcome-diagnosis "normal control". Validity of systematic paraphrenias (diagnostic stability = 0.69) was in the moderate range. Division of schizophrenias in "systematic versus non-systematic" nosological categories was inconclusive; the categories of affect-laden paraphrenia, periodic catatonia and systematic catatonias could not be confirmed reliably in this study.

Key words endogenous psychoses · Leonhardean classification · long-term follow-up · validity · affective psychoses · cycloid psychoses · schizophrenias

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Introduction

In the absence of external criteria for assessments and hypothesizing diseases as the basis of psychopathological processes, the validity of diagnoses depends on the fulfillment of the differentiated prognosis implied in the diagnoses themselves. Taking into account the concept of nosological units [19] built step by step [47], the search for so-called "small disease entities" [55], consisting of specific psychotic syndromes linked with specific outcome, represents the first phase of clinical validation studies.

The nosological significance of catamnestic studies of endogenous psychotic patients depends first and

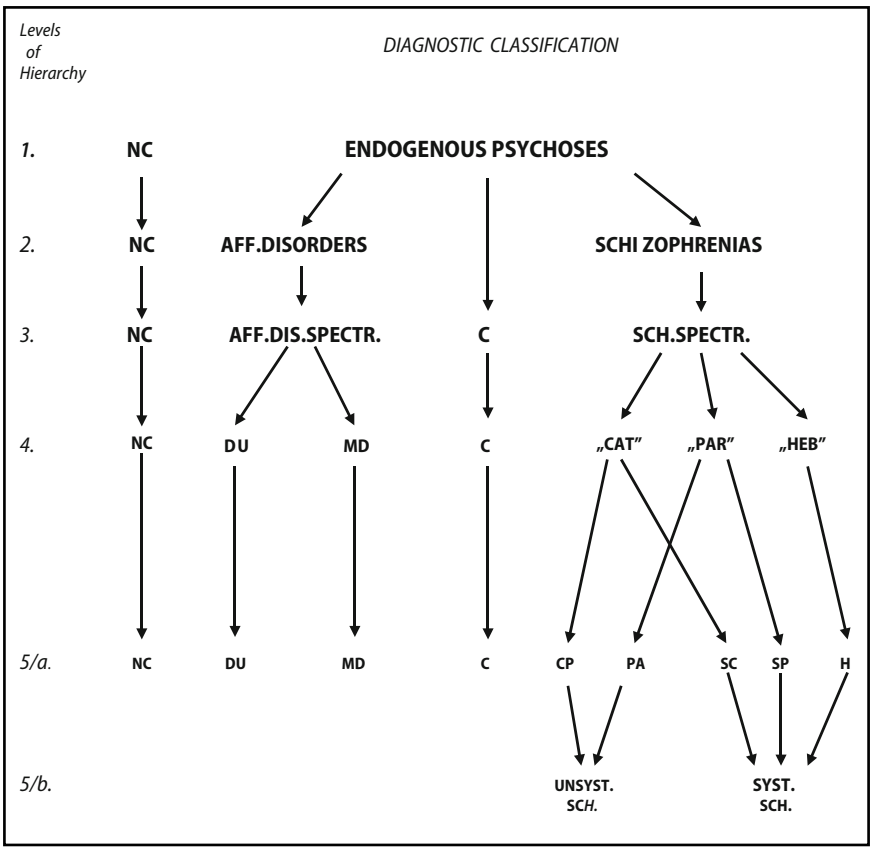

Fig. 1 Hierarchy and decision tree of the Leonhardean classification. The figure displays levels of hierarchy in the Leonhardean classification system as a rule, the diagnostic process ends at one of the categories listed at level 5 (at 5a in a "middle-level" category; or at 5b in the case no differentiation among certain middle-level categories at 5a). The diagnostic process may also end at an earlier stage (e.g., level 4 in the hierarchy). *Aff. Dis.* Affective spectrum disorder, *Sch Spectr.* schizophrenia spectrum disorder, "*CAT*" catatonia (not differentiated as "systematic"/"unsystematic"), "*PAR*" paraphrenia (not differentiated as "systematic"/"unsystematic"), "*HEB*" hebephrenia, *Unsyst. Sch.* unsystematic schizophrenias; *Syst Sch.* systematic Schizophrenias, *Spectr.* linkage of categories signed by the line between them. Cataphasia (belonging to the UNSYST. SCH.) is not represented

foremost on the symptoms identified and/or the classification specified for the starting position [16, 17]. For our prospective research project labeled "Budapest 2000" we chose Leonhard's classification [23, 25, 33, 36–39] in 1966 because diagnoses given in this system at the time of psychosis contain well-defined symptomatological descriptions and differentiated predictions concerning outcome. Testing these hypotheses may confirm or disconfirm the predictive validity of this system of classification.

We assessed a population (n = 276) of female patients with endogenous psychosis in 1967–1974 and a population of normal control persons (NC) in 1974–1976. We completed a short-term follow-up of two nosological groups in 1968–1970 [34], a 5-year re-examination in 1972–1980 [42, 43, 46, 49] and a 21–33-year follow-up (FU) of both the populations in 1997–2002 using "blind control" procedures. In this paper we present the evaluation of this FU from the point of view of the predictive validity of the nosological classification.

Methods

Subjects

For the purpose of this study, the diagnostic status of our target population was defined by one of the eight unique nosological categories representing the middle level of hierarchy in the Leonhardean classification system (see Fig. 1 below). Accordingly, eight groups of patients hospitalized in psychiatric departments for acute psychosis or for worsening of pre-existing symptoms were selected by two independent psychiatrists (one of them the principal investigator, B. P) in 1967–1974 ["index psychosis" (IND)]: unipolar depression (DU = 26), bipolar manic-depressive psychosis (MD = 27), cycloid psychoses (C = 28), affect-laden paraphrenia (PA = 30), periodic catatonia (CP = 28), systematic paraphrenias (SP = 26), systematic catatonias (SC = 25), and hebephrenias (H = 32). Patients enrolled in the study were selected to represent the nosological categories of interest for this investigation, with average number of 3.17 (SD = 2.9) prior hospitalizations.

The objective of the study was to provide a representation of each of the major diagnostic categories according to the Leonhardian system with the exception of "cataphasia" due to its estimated low prevalence in the population available for the investigation. In addition, our original intention at the time of the inception of the investigation was to include two groups of patients not classified by the Leonhardian system into any specific diagnostic class (i.e., patients with affective and schizophrenia spectrum diagnosis). However, due to budgetary and logistical reasons, enrollment of subjects into these two groups was discontinued during the investigation (these subjects were not used in the analyses due to the low sample size; n = 4 and n = 5 for the affective and schizophrenia spectrum diagnosis, respectively and for this reason data on these patients are not used for the current investigation).

The decision tree (Fig. 1) represents the structure of the Leonhardean classification.

Selection criteria at the index period (IND) were female sex, Hungarian ethnicity, an age between 14 and 55, probability of a pre-psychotic IQ of more than 75 (in operationalized form: an IQ of more than 70 is expected at time of remission of a patient), no concurrent somatic illness, no alcohol or drug dependence, hospitalization because of psychosis, and grade of remission sufficient

for discharge of the patient to her home. Normal control persons (NC; $n = 54$) were matched individually to the patients of two nosological groups (to C = NC_C, $n = 26$; to H = NC_H, $n = 28$). Since in light of the number of multiple diagnostic groups assurance of similar gender ratios would not have been feasible for the current study, female subjects were selected in order to increase the homogeneity of diagnostic groups included in the current investigation. Matched normal control subjects were selected for the cycloid and hebephrenic groups because these latter diagnostic groups were expected to represent two extremes in terms of outcome (with cycloid subjects having a substantially more favorable outcome as compared to the hebephrenic subjects).

Ratings and procedures

Patients were given the long-term catamnestic examination in 1997–2002 when they were in a condition judged by their contact persons to be their best state in the last year. Interview sessions for both patients and NC persons aiming at psycho/pathological and nosological assessments lasted 2–4 h. Diagnoses were made by the principal investigator (B.P.) and by a "blind control" psychiatrist trained previously in a psychiatric department using Leonhardean classification over a period of at least 3 years. Diagnoses at the index period were established based on semi-structured interviews conducted to identify symptoms and data on disease history characteristic of the individual nosological categories in the Leonhardian system. The diagnostic category for each patient at this time point represented a consensus decision obtained from all diagnosticians participating in the study.

Subsequently, at the 5-year re-examination and the 21–33 year follow-up, diagnoses were made by blinded psychiatrists participating in a common diagnostic session. Independent diagnostic decisions were made by each participating diagnostician after the joint diagnostic session was completed. Blinded psychiatrists were unaware of subjects' diagnostic status (i.e., control subject or patient, or prior diagnosis for patients; or history of previous or current treatments), and the diagnostic sessions were conducted in a random sequence with regard to the subjects' diagnostic status (i.e., patient or healthy control). In special cases, to establish diagnosis (e.g., unipolar depression vs. manic-depressive psychosis), data on the course of illness were available to diagnosticians upon request.

Psychopathological rating scales (RS) were administered in an identical way for investigations of patients and normal control persons during the investigation. At the time of IND, a 16-item RS that we adopted for the study was updated (Rockland Pollin Rating Scale, RPS [54]); we expanded it in 1966 (Rockland Pollin Rating Scale Expanded, RPSE [34]) to include four additional items as specified in Table 1. In addition to the RPSE, a symptom checklist consisting of 18 items each scored on a five-point scale was compiled by us (List of Specific Symptoms; LSS [34] Table 2) in order to assess symptoms not included in the RPSE, but relevant for the Leonhardean classification (e.g., detailed characterization of types of delusions and hallucinations). At the time of FU, the PANSS [21] supplemented, among others, the assessment methods.

Psychometric ratings were provided and diagnostic decisions were made at the conclusion of the diagnostic interview by diagnosticians participating in the joint interview sessions. Rating scales and the symptom checklist (i.e., list of specific symptoms) were used to record and quantify phenomenologic information that served as a basis for the diagnostic process.

Statistical analyses

Welch-d was used in the comparison of groups [61]. The kappa statistic was calculated according to Cohen [59]. We evaluated both the predictive validity of our nosological classification and the interrater reliability of the diagnoses given by the two investigators at FU by employment of a Markovian stochastic method [1, 13, 20, 60] described in earlier [58] based on a partial follow-up at the 21–33 year time point in the study.

Table 1 The Rockland Pollin rating scale, expanded version (RPSE) employed by us from 1967 for the sake of consistency throughout the entire follow-up investigation

RPSE		
Serial number	Item	Range
1	Motor activity	−9 to +8
2	Amount of facial expression	−7 to +8
3	Amount of involvement with examiner	−9 to +6
4	Appearance and dress	−9 to +3
5	Hostility (against self vs. environment)	−8 to +7
6	Speech	−9 to +7
7	Amount of affect	−9 to +7
8	Inappropriateness of affect	0 to +9
9	Mood	−7 to +8
10	Anxiety	−9 to +7
11	Thought disorder	0 to +9
12	Delusions and paranoid traits	0 to +9
13	Hallucinations	0 to +9
14	Insight	0 to +6
15	Sensorium	0 to +7
16	Judgment and abstracting ability	0 to +7
17	Emotional deficit vs. depth	−9 to +9
18	Social attitude	−9 to +9
19	Memory	−9 to +3
20	Attention	−6 to +6

The first 16 items of the RPSE were listed in Rockland and Pollin [54]
The scale was expanded by us to include items 17 through 20. In addition, item 10 was expanded to include lack of anxiety under stressful conditions
Items 1 through 7, 9, 10, and 17 through 20 are bipolar

The independent diagnostic decisions of the two diagnosticians were summarized by taking into consideration (a) the original diagnoses of the patients, (b) diagnoses given by Diagnostician 1 (B. Pethő), and (c) diagnoses given by Diagnostician 2 (who made the diagnoses "blindly" and independently: J. Tolna or M. Farkas).

Table 2 List of specific items (LSS) employed by us from 1967 throughout the entire follow-up investigation

List of specific Items (LSS)		
Serial number	Item	Range
1	Ideas of reference	0–4
2	Phonemic hallucinations	0–4
3	Visual hallucinations	0–4
4	Olfactory hallucinations	0–4
5	Somaesthetic hallucinations	0–4
6	Delusion of grandeur	0–4
7	Delusion of guilt	0–4
8	Delusion of deterioration	0–4
9	Delusion of persecution	0–4
10	Morbid jealousy	0–4
11	Erotomania	0–4
12	Fantastic delusions	0–4
13	Delusion of to be influenced	0–4
14	(By electricity, radio waves etc.)	0–4
15	Depersonalization	0–4
16	Disorganized hyperkineses	0–4
17	Paramimia	0–4
18	Parapantomimia	0–4
19	Catatonic symptoms (mannerisms, Stereotypy, ambitendency etc.)Behaves as a robot	0–4

Table 3 Distances of the nosological categories of the Leonhardean classification system and of the NC from one another in a 3-dimensional space that served as a basis for the Markov process used for the diagnostic classification

Dimensions of the a priori estimations and positions of the nosological units for the Markov process in the 3-dimensional space (initial state of the model)			
	I	II	III
C	0.6	0.9	1
H	−0.5	−1	−1
DU	0.1	1	0.5
MD	0.1	1	0.5
PA	1	0.5	0.5
CP	1	0.6	0.6
SP	1	−0.1	−0.1
SC	0.5	−0.6	−1
NC	0	0	0

The principal axes for 3-dimensional space represented three domains of interest selected by the Principal Investigator based on their relevance to the Leonhardean classification system: I: cognitive functioning; II: affect (depression/hyperthymia vs. emotional blunting); and III: the course of illness: acute vs. progressive
Interval of a dimension is −1 to +1

Based on this diagnostic information, we were faced with the problem of how to estimate reliability and validity between the nosological classification at the time of the index psychosis and the 21–33 years follow-up by Diagnostician 1 on the one hand; and on the other between Diagnosticians 1 and 2 in assigning the patients to nosological units according to the classification tree provided in Fig. 1

We followed the general ideas of Bartko and Carpenter (1976), although the methods presented in our study were extended in order to make use of Markovian stochastic model detailed below. In particular, the mathematical model employed by us can be outlined as follows.

Initially, at the beginning of the study a set of patients with psychotic disorders and control individuals were classified into certain nosological units. Let us denote the number of units by k, with $A_1, \ldots, A_k$ denoting the different units. In addition, let us denote the set of all units by U. At the end of the follow-up period, the same patients were classified by two independent evaluators. The data of a patient consist of a triplet A_i, B, C, where A_i stands for the initial nosological unit of the investigated patient and B, C are subsets of U denoting the diagnosis of the two independent evaluators (Diagnosticians 1 and 2).

At the beginning, the diagnostic status of each study subject was defined by one of the eight unique nosological disease categories representing the middle level of hierarchy in the Leonhardean classification system, and the normal controls (Fig. 1). Specifically, initially either she was diagnosed as a member of a given nosological unit, or a normal control. At the 21–33 year follow-up, her diagnostic status may have become more complex. Accordingly, the evaluators did not adopt a clear-cut diagnosis. Instead, they allowed for all the possible ones, thereby forming different possible developmental lines from nosological units ranging from normal control to the aforementioned Leonhardean categories, representing various levels of hierarchy and, in rare cases, combinations of multiple nosological units. The mathematical model used in this study makes allowance for the fact that people can cross the borders among nosological units, with the sequence of consecutive states of one person forming a Markov process.

A Markov process is a stochastic process with the property that its past and future are conditionally independent given that the present is known. In Markovian modeling framework, we considered the nosological units (Leonhardean diagnostic categories) at a given time, including both the baseline and the follow-up investigations, as subsequent states in a Markovian sequence. Based on a cross-sectional evaluation and available data regarding patient history, different diagnosticians may assign different diagnoses to a given subject, and the same diagnostician may classify patients in different nosological units at index psychosis and follow-up.

For a mathematical description of the data, we used a distribution on the subsets of one set called birthday distribution. The origin of the name is a paradox stating that among 20 independently chosen people there will almost certainly be two with the same birthday. In line with this, a Markov process results in the above-mentioned distribution. The reliability of the pair B, C is defined as the ratio of the minimum and maximum of the probabilities of the sets B, C and $B + C$. Let A and B be two sets of diagnoses. We need a measure $\Delta(A, B)$ of agreement which reflects the structure of nosological units. One natural candidate would be

$$\Delta(A,\ B) = \frac{P(A+B)}{P(A)+P(B)},$$

where P stands for probability. Formally it is acceptable, because it is between 0 and 1, but it does not meet our expectations in any other appropriate way. We must somehow measure whether ranking the same person on one occasion into subset A of nosological units and on another into subset B is a systematic or random deviation. We expect that our method will be applicable in similar cases even when there are no subsets in rankings. An additional feature of the investigated problem is that in cases where the two diagnoses differ, the discrepancy is likely to reflect an underlying change in diagnosis in the majority of cases. For example, patients classified originally DU, MD, and C are likely to be classified into the normal control group at the 21–33 year follow-up.

The aforementioned features of the diagnostic classification and its change over time led us to the following model. The status of patients was considered to follow a Markov chain (Feller 1969). In particular, over the course of years the individuals may change their status in two extreme directions. Specifically, some of the patients may undergo a near-complete recovery in the long run; other patients may deteriorate over the years. Thus, theoretically all of the possible 9×9 transitions may occur with certain probability.

The preliminary knowledge ('initial state of the model') was provided by the principal investigator for the stochastic process in the form of an estimation of the positions of the eight nosological groups in relation to NC in three psychopathological dimensions (Table 3).

Results

Patient disposition

At the time of the 21–33-year follow-up (FU) we were able to re-examine 125 patients (rediscovery rate = 56%): 95 patients had died and 2 patients were lost to follow-up (rediscovery rate of patients supposedly living = 98%; Table 4). Of the NC, 38 persons were examined at FU (rediscovery rate = 70%); 6 NC persons had died, 4 could not be traced, and 6 declined the re-examination.

Basic descriptive statistics

Table 5

Diagnostic agreeement

Diagnostic agreement between two independent reclassifiers measured by Cohen's weighted kappa was 0.87 concerning FU.

Table 4 Dropout analysis of the population investigated based on completed study

Groups of patients									
	C	H	DU	MD	PA	CP	SP	SC	$n\Sigma$
	n	*n*	*n*	*n*	*n*	*n*	*n*	*n*	
IND	28	32	26	27	30	28	26	25	222
Deceased	0	0	0	0	0	0	0	0	0
Five-year re-examination	28	32	26	27	30	28	26	25	222
Deceased	13	8	14	13	15	7	15	10	95
Lost to follow-up						1	1		2
FU	15	24	12	14	15	20	10	15	125

	Groups of normal control persons		
	NC_C	NC_H	$n\Sigma$
	n	*n*	
IND	26	28	54
Lost to follow-up	6	7	13
Fiver-year re-examination	20	21	41
Deceased	4	2	6
Lost to follow-up	2	2	4
Declined the investig.	2	4	6
FU	18	20	38

IND Index psychosis 1967–74 or first examination for NCs, *FU* long-term follow-up in 1997–2002
Our 21–33-year sample can be regarded as representative in some relevant aspects (background variables and psychopathological symptoms) in comparison with the sample of persons who died or were lost to follow-up in the period from the 5-year re-examination to the FU (Table 5)

Results of our investigation are divided into two parts: summary of observed empirical data on the one hand and on the other results obtained on the basis of the stochastic model described above.

Empirical case history from IND to FU

We arranged the two diagnoses of each person given by the two independent investigators at FU on a dyadic tree (Fig. 2) derived from the decision tree (Fig. 1). This dyadic tree served as a basis for the analysis of diagnostic reclassification presented subsequently in Table 6.

The nine diagnostic units used both at IND and at FU (Fig. 1, Level *5/a*) are listed in the middle of dyadic tree. The first new vertex, the tenth vertex in the series of the diagnoses 1–9 considered as vertices of the dyadic tree, is the unity of the leaves 7 (= SP) and 8 (= SC). We describe this subset consisting of these two categories (7 and 8) in a concise form as 10(7,8). To this subset belong the cases considered by a diagnostician to be diagnosed on the basis of the interview session as either "systematic paraphrenia" or "systematic catatonia" but with the diagnostician being unable to decide on which. Similarly, we united leaves 3 and 4 into a new vertex labeled No. 11, and leaves 5 and 6 into No. 12. Using our formula, these vertices are described as 11(3,4) and 12(5,6). Note that only subset 12(5,6) occurred among the three subsets mentioned (Nos. 10–12) in our sample, but subsets No. 10 and No. 11 are considered also as intermediate vertices between the nine original categories on the one hand and some more complex subsets on the other. For example, in the next step we united the nosological category 2 (= H) with the subset No. 10 already formed. This subset described as 13(2,10) represents the nosological category "systematic schizophrenia" consisting of the three "middle-level" categories H, SP and SC. Proceeding in the same way, we formed the new vertex No. 14 from the already-defined vertices No. 1 and No. 11, No. 15 from No. 12 and No. 13 ["Schizophrenia": collective term for PA, CP, SP, SC, and H if the diagnostician ascends from these middle-level categories upwards on the decision tree (Fig. 1) or an undifferentiated state of illness if the diagnostician descends starting from the term "psychosis"] and No. 16 from No. 14 and No. 15. Vertices of subsets 17(1,9), 18(1,6), 19(6,8), 20(5,7), and 21(1,12) are represented below the line of the nine original categories (Nos.1–9).

Persons belonging to the subsets occurring at FU were recruited from the groups of the nine categories at IND. Rearrangement of the FU subsets according to the IND groups the patients of these subsets were recruited from is shown in Table 6. In the subsets, the diagnosis given by the two independent diagnosticians in agreement is indicated by the serial numbers of the nosological categories (Fig. 2) in the brackets, e.g. (1,1), (2,2), (15,12). These diagnoses in an identical row [e.g. (1,1) in the row of C (= 1)] indicate direct stability of the IND diagnosis in question from IND to FU, i.e. they indicate the agreement of the two diagnosticians in recognition of a patient's belonging to the same nosological category at FU as the one s/he belonged to at IND (e.g. C = 3/15 = 20%).

Table 5 Basic background variables (mean ± SD) of the study sample at 5-year re-examination

Variables/ Nosological groups		n	Age at onset of the illness	Education (number of school years complete)	Symptom severity on RPS[a]			Full Wechsler-IQ	ECT (sum of treatments)	Neuroleptics	Antidepressive treatment	Age
					General appearance Items 1–6	Affectivity Items 7–10	Cognitive functioning items 11–16					
C	Inv	15	27.7 ± 9.2	11.6 ± 2.4	3.4 ± 3.4	1.7 ± 1.4	0.6 ± 1.2	113.2 ± 13.	12.8 ± 9.7	1.6 ± 1.1	0.2 ± 0.6	35.4 ± 11.6
	Dis	13	33.9 ± 8.9	10.1 ± 3.3	2.6 ± 2.0	1.5 ± 1.3	1.0 ± 1.8	102.8 ± 13.8	21.4 ± 23.4	1.6 ± 0.7	0.0 ± 0.0	44.8 ± 11.8*
H	Inv	23	20.0 ± 4.2	11.3 ± 2.0	15.4 ± 7.2	7.9 ± 3.9	10.3 ± 5.4	98.4 ± 11.1	30.1 ± 22.4	2.1 ± 0.9	0.0 ± 0.2	29.3 ± 4.3
	Dis	8	24.7 ± 3.0**	11.3 ± 4.2	13.8 ± 8.3	6.7 ± 2.8	7.5 ± 6.3	101.1 ± 15.6**	28.0 ± 17.7	1.3 ± 1.1	0.1 ± 0.3	35.0 ± 4.6*
DU	Inv	12	37.0 ± 13.8	11.0 ± 4.1	1.8 ± 1.9	1.5 ± 1.7	0.2 ± 0.6	105.0 ± 12.5	1.6 ± 2.5	0.5 ± 1.1	0.1 ± 0.5	47.5 ± 11.3
	Dis	14	40.8 ± 11.4	10.0 ± 3.0	1.3 ± 1.2	1.4 ± 1.0	0.3 ± 0.6	107.5 ± 14.3	10.6 ± 16.1	0.7 ± 0.8	0.7 ± 1.2	51.2 ± 7.4
MD	Inv	14	26.9 ± 9.2	12.0 ± 2.4	2.7 ± 2.5	1.5 ± 1.2	0.1 ± 0.5	108.7 ± 11.3	11.9 ± 15.7	1.4 ± 0.7	0.4 ± 0.7	38.3 ± 11.3
	Dis	13	34.4 ± 11.9	13.3 ± 3.0	2.6 ± 2.4	2.0 ± 1.6	0.1 ± 0.3	104.4 ± 10.5	17.0 ± 14.4	0.8 ± 0.9	0.6 ± 0.8	50.3 ± 11.3*
PA	Inv	15	30.2 ± 6.3	13.3 ± 3.8	7.3 ± 3.6	3.8 ± 2.5	10.4 ± 7.6	106.2 ± 13.7	25.9 ± 17.6	1.8 ± 1.1	0.1 ± 0.3	39.9 ± 6.8
	Dis	15	38.0 ± 8.2**	11.9 ± 2.8	8.4 ± 3.3	4.2 ± 2.0	12.0 ± 7.2	104.7 ± 10.9	14.6 ± 5.2*	1.6 ± 1.1	0.0 ± 0.2	47.6 ± 8.3**
CP	Inv	20	25.6 ± 8.2	11.5 ± 3.2	12.3 ± 6.2	2.4 ± 2.2	4.3 ± 2.7	104.6 ± 12.3	24.3 ± 13.8	2.5 ± 1.2	0.1 ± 0.5	36.0 ± 9.2
	Dis	8	35.7 ± 6.4**	10.6 ± 3.7	12.2 ± 7.7	4.6 ± 3.6	8.2 ± 5.8	94.8 ± 13.6**	28.2 ± 24.2	2.1 ± 1.2	0.1 ± 0.3	48.2 ± 5.1**
SP	Inv	10	38.1 ± 9.2	8.4 ± 2.5	8.6 ± 4.3	3.2 ± 2.8	11.6 ± 5.6	99.1 ± 14.7	7.6 ± 8.8	1.5 ± 0.9	0.0 ± 0.0	48.5 ± 7.6
	Dis	16	36.6 ± 10.3	8.2 ± 3.7	7.0 ± 3.9	3.7 ± 1.9	14.3 ± 8.8	97.6 ± 10.0	8.6 ± 9.2	1.6 ± 1.0	0.1 ± 0.5	51.1 ± 8.4
SC	Inv	15	28.9 ± 8.2	11.6 ± 2.7	14.8 ± 7.1	4.8 ± 2.6	7.6 ± 5.2	96.7 ± 11.7	17.8 ± 16.8	2.1 ± 1.1	0.0 ± 0.0	38.6 ± 8.5
	Dis	10	28.4 ± 8.2	12.8 ± 4.0	15.7 ± 8.3	4.5 ± 1.4	9.1 ± 7.5	98.0 ± 18.4	13.6 ± 12.6	2.8 ± 0.9	0.2 ± 0.6	41.8 ± 10.1
NC	Inv	32	–	12.5 ± 2.8	2.3 ± 2.6	1.0 ± 0.6	0.1 ± 0.4	112.1 ± 12.9	–	–	–	34.8 ± 7.6
	Dis	9	–	11.7 ± 2.6	1.6 ± 1.8	1.2 ± 1.2	1.3 ± 1.3	111.2 ± 10.8	–	–	–	40.7 ± 10.3

Since patients in this investigation were in a stable condition at the 5-year re-examination period (as compared to the index evaluation) which permitted to administer the full test battery (including the assessment of IQ) data from this period are shown in this table

ECT Electroconvulsive therapy; number of treatments, *Dis* deceased or lost to follow-up from IND to FU, *Inv* available at long-term follow-up

Significance (nominal *P*-values based on Welch-d for Dis vs. Inv) indicated in the second row (Dis and Inv) of the each nosological category compared to one another: * $P < 0.05$, ** $P < 0.01$

[a]Symptom severity on the RPS, with higher scores indicating greater impairment

Summarizing the diagnostic re-classification data at the follow-up displayed in Table 6 indicates that the diagnostic stability in this strict sense is different in the nine categories: DU = 3/12 = 25%; MD = 4/14 = 29%; C = 3/15 = 20%; PA = 3/15 = 20%; CP = 9/20 = 45%; SP = 5/10 = 50%; SC = 8/15 = 53%; H = 20/24 = 83%; NC = 34/38 = 89%.

With regard to the various outcomes in terms of re-classification, identification of a patient in Table 6 as a "NC" indicated "full recovery" at follow-up. For example, (9,9):*6* in row C (Table 6) means that six patients (40%) diagnosed at IND with "Cycloid psychosis" recovered to such an extent that the two independent diagnosticians could not distinguish them from the NC persons.

In addition, two C patients were diagnosed as "NC" in disagreement, indicated by (1,9) and (9,4) in Table 6, respectively. Counting "NC" diagnosis in disagreement as partial agreement with a score of 0.5, 6 + ½ + ½ = *47%* of C patients were recovered. Full recovery in this latter sense occurred not infrequently in the two affective groups [DU = 17/*33%* (italics refer to percentage including "NC" diagnosis in disagreement), MD = 21/*29%*] and in C (40/*47%*) but occurred hardly at all in the schizophrenic groups (PA = 0/*3%*, CP = 0/*0%*, SP = 0/*0%*, SC = 12/*12%*, H = 0/*4%*).

As Table 6 indicates, change of the diagnosis from the groups (DU, MD, C) to schizophrenic groups (PA,

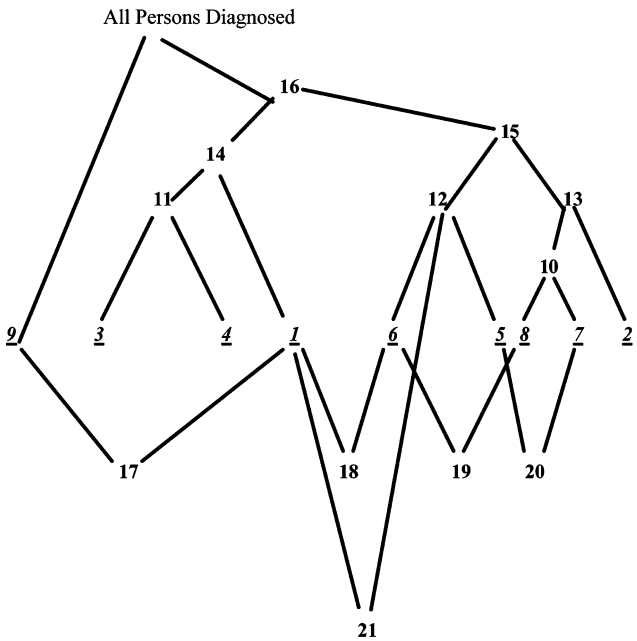

Fig. 2 Diagnoses of each person given by the two independent investigators at FU: Arrangement on a dyadic tree. Numbers *1–9* (*middle row*, italics) indicate the nine diagnostic categories at IND (in 1967–1976, Table 4) recognized by the diagnosticians at FU in agreement. Numbers 10–21 indicate the cases diagnosed by the two independent diagnosticians either differently from the persons' diagnosis at IND and/or in disagreement at FU. Numbers *17–21* are featured below the row of the line of the categories *1–9*. List of the diagnoses (the character "/" = "either/or")

Table 6 Nosological assessment made by the two independent diagnosticians at FU

Diagnoses at IND		Diagnoses at FU	Total number of persons
1	C	(1,1): **3**, (9,9): **6**, (3,3): **1**, (4,4): **1**, (1,9): **1**, (9,4): **1**, (1,11): **1**, (14,1): **1**	15
2	H	(2,2): **20**, (2,13): **2**, (2,9): **1**, (2,8): **1**	24
3	DU	(3,3): **3**, (9,9): **2**, (2,2): **1**, (9,3): **2**, (3,9): **1**, (5,7): **1**, (9,1): **1**, (9,4): **1**	12
4	MD	(4,4): **4**, (9,9): **3**, (9,4): **3**, (4,9): **3**, (2,2): **1**	14
5	PA	(5,5): **3**, (7,7): **3**, (8,8): **1**, (13,13): **1**, (5,7): **1**, (16,12): **1**, (15,2): **1**, (15,12): **1**, (6,12): **1**, (5,20): **1**, (21,9): **1**	15
6	CP	(6,6): **9**, (8,8): **2**, (5,5): **1**, (6,5): **1**, (6,8): **1**, (8,2): **1**, (6,11): **1**, (12,13): **1**, (17,17): **1**, (8,19): **1**, (6,18): **1**	20
7	SP	(7,7): **5**, (13,13): **1**, (7,5): **1**, (5,7): **1**, (7,15): **1**, (8,15): **1**	10
8	SC	(8,8): **8**, (2,2): **2**, (9,9): **1**, (8,6): **1**, (8,13): **1**, (7,13): **1**, (7,2): **1**	15
9	NC	(9,9): **34**, (9,1): **1**, (1,9): **1**, (9,3): **1**, (13,13): **1**	38

Diagnoses at FU are listed in respect of the nine nosological categories at IND
Numbers 1–9 listed both in the first column and in brackets in the third column refer to the serial number of the nine diagnoses (Table 4) used both at IND at FU
Numbers 10–21 refer to the steps (Fig. 2) ordering the cases diagnosed by one or two independent diagnosticians differently from the index diagnoses or in disagreement at FU
The first number in the brackets refers to the diagnostician **A** (= B. P.) while the second number refers to the diagnostician **B** (J. T. or M. F.)
The bold face number after the colon following a bracket refers to the number of persons diagnosed in the category defined by the two numbers in the bracket

CP, SP, SC, H) and vice versa occurred rarely from IND to FU (2 cases = 5% vs. 2.5 cases = 3%).

Concerning the re-classification of NC subjects, only one subject was re-diagnosed at the follow-up by both independent investigators other than "NC" in agreement (as "13": Spectrum of systematic schizophrenias; 3%) and three in disagreement (one person as DU = 3%; two persons as C = 5%).

Table 7 presents the re-classification summary of patients at 21–33 year follow-up as compared to the index period according to congruent and incongruent diagnostic categories using the Leonhardian system. Diagnostic category at re-classification was considered as congruent with initial classification if at least one of the raters classified the patient in the original diagnostic category assigned at the index period.

Stochastic model of the case histories from IND to FU

In comparison with the empirical case histories, the virtual transitions (Table 8) indicate a little higher stability of the diagnoses on one hand and their more detailed distribution in other categories on the other. However, the distribution of the diagnoses is congruent with the outcomes observed empirically (Table 6).

As regards the trends of the manifestation of the IND diagnoses at FU (Table 8), two extremes can be observed. First, H at FU is over-represented on the basis of the sum of the probabilities of transition of the IND diagnoses (mainly of the SC) into H (Summa = 1.510, in last row in Table 8). Second, NC at FU is over represented on the basis of the summed probabilities of transition of IND diagnoses (mainly DU, MD and C) into NC (Summa = 1.757, indicating a trend of recovery). In contrast, some IND diagnoses are under-represented at FU (summa of transition probabilities less than one), mainly also on the basis of the trend of recovery on the one hand (DU, C, MD) and of nosological uncertainty (PA, CP) on the other.

Concerning MD and C, their low single-category validity (MD = 0.563, C = 0.475) reflecting no so specific residual was improved by the probability of their re-classifications into NC, reflecting full recovery implied in both of their respective nosological diagnosis. Predictive validity of MD (i.e., MD + NC) and C (C + NC) was 0.77 and 0.76, respectively.

Taking into consideration the generally favorable outcome of the groups DU, MD and C at FU, as expected by the Leonhardean nosological system, transition of a DU, MD or C patient to the other one or two groups of this diagnostic triplet was also not "wrong" but rather a finding, reflecting an improved validity by comprising a "non-specific affective residual". Group probabilities of single-category predictive validity in this sense (i.e., probability of classification of DU, MD, C or NC into their own categories) were as follows: DU = 84% (instead of its single-category probability 34% and instead of the DU + NC two-category validity = 58%); MD = 93% (instead of its single-category probability 56%); and C = 93% (instead of its single-category probability 48%). These group probabilities were at the level of the single-category probability of the reclassification of the NC persons within their own category (NC = 91%).

Among the schizophrenic categories, probabilities of the re-classification of PA into SP (= 27%), CP into SC (= 15%) and SP into PA (= 17%) were not low, but reclassification of SC into CP was improbable (5%). Improbable, too, was the reclassification of a patient belonging originally to one of the schizophrenia groups into the NC group (PA = 3%, CP = 3%, SP = 1%, SC = 3%, H = 2%).

In contrast to the groups DU, MD and C, a favorable outcome (transition to NC) is not posited in the Leonhardean system for the five nosological categories of the schizophrenias (PA, CP, SP, SC, H), which are expected to remain distinct throughout the course

Table 7 Re-classification summary of patients at 21–33 year follow-up as compared to the index period according to congruent and incongruent diagnostic categories using the Leonhardian system

Diagnoses at IND	*n*	No change in diagnostic status (*n*/%)	Re-classified as	
			Congruent (*n*/%)	Incongruent (*n*/%)
C	15	15 (100)	0 (0)	0 (0)
H	24	24 (100)	0 (0)	0 (0)
DU	12	10 (83.3)	2 (16.7)	0 (0)
MD	14	13 (92.9)	1 (7.1)	0 (0)
PA	15	9 (60)	5 (33.3)	1 (6.7)
CP	20	15 (75)	2 (10)	3 (15)
SP	10	10 (100)	0 (0)	0 (0)
SC	15	11 (73.3)	1 (6.7)	3 (20)
NC	38	37 (97.4)	1 (2.6)	0 (0)

Diagnostic category at re-classification was considered as congruent with initial classification if at least one of the raters classified the patient in the original diagnostic category assigned at the index period

of the disease. Nonetheless, from the perspective of a less differentiated diagnosis according to the Leonhardean classification (see Level 3 of hierarchy on Fig. 1), all five categories are characterized by poor outcome, which provides a rationale for pooling these categories in order to investigate their predictive validity. Based on this approach, the predictive validity of these five categories of schizophrenias is supported by the high probability (93%) of re-classification for the group of schizophrenias, taken together (i.e., probability of reclassification of diagnostic group at level *5/a* (Fig. 1) into itself, or the probability of re-classification into any of the four remaining level *5/a* diagnostic category of schizophrenias). Reclassification of any one of the five individual schizophrenic categories into the DU, MD and C categories was unlikely (e.g., the probability of reclassification of SC into DU, MD and C was 0.011, 0.015 and 0.015, respectively). Thus, patients from these categories (i.e., schizophrenias) showed a low likelihood of transition to the DU, MD, C on the one hand or to the normal group on the other (Table 8).

Based on the Leonhardean system (see Level *5/a* on Fig. 1), there was no theoretical rationale to pool probabilities of reclassification among the five nosological categories of the schizophrenias (PA, CP, SP, SC, H) between each other because these are distinctly different nosological units. However, at a less differentiated stage of the classification involving more general diagnostics categories (see Level 3 on Fig. 1), a substantial improvement of the predictive validity of the nosological categories of the schizophrenias (PA, CP, SP, SC, H) was detectable by pooling probabilities of reclassification among these five categories between each other (probability of reclassification = 0.93).

Discussion

Even the Kraepelinian dichotomy of affective versus schizophrenic psychoses (Dementia praecox) [22], which has been adopted as a common view in psychiatry, was both revised and confirmed from time to time in respect of syndromatology [3], of long-term outcome chronicity [7] and of "insufficiency syndrome" [52] and/or of negative symptoms [15,29]. This dichotomy of endogenous psychoses characterized by recovery versus non-recovery was corroborated by our findings.

The validity of the Leonhardean division of affective psychoses into unipolar depression and bipolar manic-depressive psychoses was reported earlier [2, 4]. We found weak single-category validity of DU and MD measured by their diagnostic stability from IND to FU, but we validated MD by including full recovery and DU by forming a "nosological family" based on diagnostic stability, on current status and clinical presentation during the period preceeding the follow-up with regard to other mood-congruent disorders

Table 8 Probabilities of the stochastic transitions in the Markov model

FU	C	H	DU	MD	PA	CP	SP	SC	NC	∑
IND										
C	**0.475**	0.048	0.080	0.091	0.006	0.001	0.008	0.007	0.283	≈1.00
H	0.004	**0.938**	0.002	0.004	0.001	0.000	0.002	0.031	0.017	≈1.00
DU	0.162	0.079	**0.341**	0.095	0.027	0.010	0.020	0.023	0.243	≈1.00
MD	0.111	0.056	0.050	**0.563**	0.002	0.002	0.003	0.011	0.202	≈1.00
PA	0.030	0.065	0.036	0.011	**0.449**	0.034	0.271	0.069	0.033	≈1.00
CP	0.019	0.086	0.031	0.022	0.062	**0.543**	0.051	0.152	0.033	≈1.00
SP	0.013	0.043	0.007	0.004	0.170	0.007	**0.685**	0.058	0.013	≈1.00
SC	0.015	0.189	0.011	0.015	0.032	0.053	0.069	**0.588**	0.027	≈1.00
NC	0.057	0.006	0.012	0.019	0.000	0.000	0.000	0.000	**0.906**	≈1.00
∑	0.886	1.510	0.570	0.824	0.749	0.650	1.109	0.939	1.757	

Bold numbers: one-to-one diagnostic stability; transition probabilities (i.e., correct reclassification) for all categories exceeded the chance level at the level of statistical significance ($P < 0.05$)

Italics: group belonging to the family of the nosological category indicated by italics in the same row (among the schizophrenic groups only two relationships are indicated: "paraphrenia" on the one hand and "catatonia" on the other).

Summa of values in a column indicates the trend of the manifestation of the diagnosis indicated in the upper row of the same column (Summa >1.0 indicates a strong trend, Summa <1.0 indicates a weak trend)

and outcome-classification as "normal control". For example, DU patients without current symptom manifestations who were classified retrospectively in the MD or the C classes by the blind diagnostician were considered as representing the same nosological family.

Results of researches concerning the syndromatology, course and outcome of nosological entities of schizophrenia are much more controversial than results of researches concerning nosological entities of affective psychoses. As regards catatonia, there is even the issue of its disappearance [56] on the one hand, and the presentation of arguments for its Leonhardean classification [31, 53, 57] on the other. European long-term follow-up studies completed before 2000 [11, 14, 18, 29] focused more on symptomatology than on detailed nosological entities. An overview of current classification systems including ICD-10 and DSM-IV (and DSM-III-R) urges validation studies [9].

In the present study, we were able to provide evidence for the existence of two nosological categories (C and H) that are not properly defined, or are even neglected, in some other classification systems. The nosological validity of the Cycloid psychoses [24, 41] was previously both demonstrated [6, 27, 30, 32] and questioned [8]. We validated it by considering full recovery, and, more importantly, by constructing a "nosological family" to cover the spectrum of its long-term outcome including nosospecific residual, affective residual (measured by cross-diagnoses with DU and MD) and full recovery. The other nosological category validated in this study at the long-term outcome is the hebephrenias [35].

Furthermore, we furnished evidence for the existence of SP as a separate nosological entity. Concerning the "systematic versus non-systematic" division of schizophrenias validated earlier [10] in respect of heredity and course of illness was inconclusive.

As regards the complex question concerning (1) diagnostic correctness/error (epistemological question), (2) nature of illness (ontological question) and (3) history of disease entities (question of processes), we emphasize three facts: (a) recognition of identical IND diagnoses in agreement at FU verifies nosological categories; (b) FU diagnoses which are discordant with respect to IND diagnoses (20% in the population of patients) suggest a change in the course of illness rather than diagnostic mistakes; (c) similarly, FU diagnoses that are not specific in comparison with the IND diagnoses (11% in the population of patients; e.g. diagnosis only "schizophrenia" at FU in cases diagnosed as "systematic paraphrenia" at IND; cf. Fig. 1 and Table 6) indicate a dedifferentiation of the nosological categories rather than diagnostic errors since they were based on diagnostic agreement.

Simultaneously, a series of questions to be answered arises concerning (1) the difference between psychopathological symptoms and "uncharacteristic" residues [12, 18]; (2) the difference between clinical recovery and social fitness; (3) the difference between scope and type of knowledge operationalized for the identification of nosological categories on the one hand and the scope and type of knowledge necessary for classifying persons with regard to their social functioning on the other; and (4) associations between types of psychoses and course of illnesses on the one hand and levels and types of outcome on the other.

Conclusion

Classification of endogenous psychoses elaborated by the Wernicke–Kleist–Leonhard school never belonged to the mainstream of psychiatry and does not belong to it today [6]. However, detailed observation, as well as experiential phenomenology, strict criteria of identification of illnesses, prediction of outcome involved in the diagnoses of psychotic states, and insistence upon hypotheses of biological etiology (besides the psychosocial etiopathogenesis) of psychoses give heuristic value to investigations based on this classification. In the first stage of the process of analyses of our data presented in this paper, we validated four of the eight middle-level categories of this system of classification as "small disease entities", and we found that the other four categories deserve attention in subsequent validation studies.

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References

1. Albert PS, Waclawiw MA (1998) A two-state Markov chain for heterogeneous transitional data: a quasi-likelihood approach. Stat Med 17(13):1481–1493
2. Angst J (1980) Verlauf unipolar depressiver, bipolar manisch-depressiver und schizo-affektiver Erkrankungen und Psychosen. Ergebnisse einer prospektiven Studie. Fortschr Neurol Psychiatr 48:3–30
3. Angst J (2002) Historical aspects of the dichotomy between manic-depressive disorders and schizophrenia. Schizophr Res 57(1):5–14
4. Angst J, Perris C (1968) Zur Nosologie endogener Depressionen. Vergleich der Ergebnisse zweier Untersuchungen. Arch Psychiatr Nervenkr 210:373–386
5. Beckmann H (1995) Leonhard's nosology in psychiatric research—recent results. In: Beckmann H, Neumärker K-J (eds) Endogenous psychoses. Leonhard's impact on modern psychiatry. Ullstein/Mosby, Berlin Wiesbaden, pp 4–13
6. Beckmann H, Bartsch AJ, Neumärker KJ et al (2000) Schizophrenias in the Wernicke-Kleist-Leonhard school. Am J Psychiatry 157:1024–1025
7. Benazzi F (1999) Bipolar II versus unipolar chronic depression: a 312-case study. Compr Psychiatry 40(6):418–421
8. Brockington IF, Roper A, Buckley M et al (1991) Bipolar disorder, cycloid psychosis and schizophrenia: a study using

"lifetime" psychopathology ratings, factor analysis and canonical variate analysis. Eur Psychiatr 6:223–236
9. Editorial (2002) Wanted: validation studies on the current diagnostic classifications. Acta Psychiatr Scand 106:81–82
10. Franzek E, Beckmann H (1992) Schizophrenia: Not a disease entity? A study of 57 long-term hospitalized chronic schizophrenics. Eur J Psychiatry 6(2):97–108
11. Gross G, Huber G, Schüttler R (1986) Long-term course of Schneiderian schizophrenia. In: Marneros A, Tsuang MI (eds) The schizoaffektive psychoses. Springer, Berlin, pp. 179–187
12. Gross G, Huber G (2000) The long-term outcome of schizophrenic and related disorders. a critical review.Neurol Psychiatr Br 8:121–130
13. Hastie T, Tibshirani R, Friedman J (2001) The elements of statistical learning. Data mining, inference and prediction. Springer, Berlin
14. Häfner H, an der Heiden W (1999) The course of schizophrenia in the light of modern follow-up studies. Eur Arch Psychiatry Clin Neurosci 249(Suppl. 4):IV/14–IV/26
15. Herbener ES, Harrow M (2001) Longitudinal assessment of negative symptoms in schizophrenia/schizoaffective patients, other psychotic patients, and depressed patients. Schizophr Bull 27(3):527–537
16. Huber G (1966) Reine Defektsyndrome und Basisstadien endogener Psychosen. Fortschr Neurol Psychiatr 34:409–426
17. Huber G (1992) The phenomenological approach to major psychoses in Europe during the past several decades. Neurol Psychiatr Brain Res 1:49–53
18. Huber G (1997) The heterogeneous course of schizophrenia. Schizophr Res 28:177–185
19. Jaspers K (1959) Allgemeine Psychopathologie. 7. Auflage. Springer, Heidelberg
20. Juang BH, Rabiner LR (1991) Hidden markov models for speech recognition. Technometrics 33:251–272
21. Kay SR, Opler LA, Fiszbein A (1992) The positive and negative syndrome scale (PANSS) manual. Multi-Health Systems, Toronto
22. Kraepelin E (1896) Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. 5.Auflage. Barth JA, Leipzig
23. Leonhard K (1957) Aufteilung der endogenen Psychosen. Akademie, Berlin
24. Leonhard K (1961) Cycloid psychoses—endogenous psychoses wich are neither schizophrenic nor manic-depressive. J Ment Sci 107:633–649
25. Leonhard K (1979) The classification of endogenous psychoses, 5th edn. In: Robins E (ed) Berman R Trans. Irvington Publ. New York
26. Lindwall M, Hagnell O, Ohman R (1986) Epidemiology of cycloid psychosis. A prospective longitudinal study of incidence and risk in the 1947 cohort of the Lund by study. Eur Arch Psychiatry Neurol Sci 236(2):109–118
27. Maj M (1990) Cycloid psychotic disorder: validation of the concept by means of a follow-up and a family study. Psychopathology 23:196–204
28. Moriarty PJ, Lieber D, Bennet A, White L, Parrella M, Harvey PD, Davis KL (2001) Gender differences in poor outcome patients with lifelong schizophrenia. Schizophr Bull 27(1):103–113
29. Möller H-J, Bottlender R, Gross A, Hoff P, Wittmann J, Wegner U, Strauss A (2002) The Kraepelinian dichotomy: preliminary results of a 15-years follow-up study on functional psychoses: focus on negative symptoms. Schizophr Res 56:87–94
30. Peralta V, Cuesta MJ, Serrano JF, Martinez-Larrea JA (2001) Classification issues in catatonia. Eur Arch Psychiatry Clin Neurosci 251(Suppl. 1):114–116
31. Peralta V (2003) Cycloid psychosis: a clinical and nosological study. Psychol Med 33:443–453
32. Perris C (1974) A study of cycloid psychoses. Munksgaard, Copenhagen
33. Pethő B (1969) Zur methodologischen Neubesinnung in der Psychiatrie. I. Mitteilung: Von der Entwicklung einiger psychiatrischer Richtungen mit besonderer Rücksicht auf ihr Relationssystem sowie. auf die Methoden des Verstehens und des Erklärens. Fortschr Neurol Psychiatr 37:405–447
34. Pethő B (1972a) Differentiated diagnostics of cyloid psychoses and hebephrenias: a study of validity of psychiatric nosology. PhD Thesis, Hungarian Academy of Sciences, Budapest (Hungarian)
35. Pethő B (1972b) Hundert Jahre Hebephrenie. Psychiatr Neurol Med Psychol 24:305–317
36. Pethő B (1974a) Einige in nosologischer Beziehung bedeutende Aspekte der Schizophrenie-Frage. I. Mitt. Die Auflösung der nosologischen Kategorie der Schizophrenie und die Wege ihrer Festigung. Psychiatr Neurol Med Psychol 26:136–143
37. Pethő B (1974b) Einige in nosologischer Beziehung bedeutende Aspekte der Schizophrenie-Frage. II. Mitt.: Von der Entwicklung und der Rolle der gehirnpathologisch orientiertenpsychiatrischen Richtung. Psychiatr Neurol Med Psychol 26:211–216
38. Pethő B (1974c) Einige in nosologischer Beziehung bedeutende Aspekte der Schizophrenie-Frage. III. Mit. Wege und Formen der Weiterentwicklung der Schizophrenielehre der gehirnpathologisch orientierten psychiatrischen Richtung. Psychiatr Neurol Med Psychol 26:321–331
39. Pethő B (1974d) Zur methodologischen Neubesinnung in der Psychiatrie. II. Mitt. Von der Entwicklungsgeschichte der pschichiatrischen Nosologie und von den aktuellen Problemen ihrer Weiterenwicklung. Fortschr Neurol Psychiatr 42:475–538
40. Pethő B (1975) Le milieu social et les symptoms de deux groupes de schizophrènes. Ann Méd psychol 133:153–166
41. Pethő B (1983) Concepts of schizo-affective psychoses. History, construct validity and some empirical data. Psychiatr Clin 16:71–86
42. Pethő B (1984) Hourglass model of psychiatric diseases: the endogenous psychoses. Schizophr Bull10:509–519
43. Pethő B (1986) An intrinsic way of multiclassification of endogeneus psychoses. A follow-through investigation (Budapest 2000) based upon Leonhard classification. In: Seidel K, Neumarker K-J, Schulze HA (eds) Zur Klassifikation endogener Psychosen. Hirzel, Leipzig, pp 67–83
44. Pethő B (1988) Depth Dimension. A psychometric approach and some clinical data. Psychopathology 21:122–125
45. Pethő B (1990) Development and structure of the DCR Budapest-Nashville. In: Beckmann H, Lanczik M (eds) Leonhard classification of endogenous psychoses, Psychopathology, vol 23. Karger, Basel, pp 316–330
46. Pethő B (2001) Klassifikation, Verlauf und residuale Dimension der endogenen Psychosen. Fünfjährige katamnestische Untersuchungen im Rahmen eines kontrollierten prospektiven Forschungsprojekts ("BUDAPEST 2000"). Mit 15 Abbildungen und 44 Tabellen Vorwort von Gerd Huber. Platon Publ. Budapest. Universitätsverlag. Ulm
47. Pethő B, Horváth Szabó K, Mórotz K, Hajtman B, Sajgóné Molnár I (1976) Residuale Dimension und Defekt. Schweiz Arch Neurol Neurochir Psychiatr 119:275–280
48. Pethő B, Tolna J, Tusnády G (1979) Multi-trait—multi-method assesment of predictive variables of outcome in schizophrenia spectrum disorders. A nosological evaluation. J Psychiatr Res 15:163–174
49. Pethő B, Ban T, Kelemen A, Ungvári G, Karczag I, Bitter I, Tolna J, Jarema M, Ferrero F, Aguglia E, Zurria GL, Fjetland O (1988) DCR Budapest-Nashville in the diagnosis and classification of functional psychoses. Psychopathology 21:153–240
50. Pethő B, Kelemen A, Bitter I, Karczag I, Tolna J (1995) Budapest 2000: first validation of Leonhard's middle groups of endogenous psychoses. In: Beckmann H, Neumarker K-J (eds) Endogenous psychoses. Leonhard's impact on modern psychiatry. Ullstein/Mosby, Berlin Wiesbaden, pp 83–90
51. Pethő B, Tolna J, Tusnády G, Farkas M, Vizkeleti G, Marosi J (2002) Basic symptoms: a long-term follow-up. Neurol Psychiatr Brain Res 9(4):191–196
52. Petrilowitsch N (1969) Insuffizienz-syndrome bei abklingenden schizophrenen und zyklothymen Psychosen. In: Huber G (ed) Schizophrenie und Zyklothymie. Ergebnisse und Probleme. Thieme, Stuttgart, pp 114–124

53. Pfuhlmann B, Stöber G (2001) The different conceptions of catatonia: historical overview and critical discussion. Eur Arch Psychiatry Clin Neurosci 251(Suppl. 1):14–17
54. Rockland IH, Pollin W (1965) Quantification of psychiatric mental status. Arch Gen Psychiatry 12:23–28
55. Schneider K (1925) Wesen und Erfassung der Schizophrenen. Zeitschrift der gesamten Neurologie und Psychiatrie 99:542–547
56. Stompe T, Ortwein-Swoboda G, Ritter K, Schanda H, Friedmann A (2002) Are we witnessing the disappearance of catatonic schizophrenia? Compr Psychiatry 43(3):167–174
57. Stöber G (2001) Genetic predisposition and environmental causes in periodic and systematic catatonia. Eur Psychiatry Arch Clin Neurosci 251(7):121–124
58. Tolna J, Pethő B, Farkas M, Vizkeleti Gy (2001) Validity and reliability of Leonhard's classification of endogenous psychoses. J Neural Transm 108:629–636
59. Thompson JR (2001) Estimating equations for kappa statistics. Statist Med 20:2895–2906
60. Tusnády GE, Tusnády G, Simon I (1995) Independence divergence generated binary trees of amino acids. Protein Eng 8(5):417–423
61. Wilcox RR (1996) Statistics for the social sciences. Academic Press, San Diego, New York