Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Empirical validity of Leonhard's psychoses: A long-term follow-up study of first-episode psychosis patients

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ARTICLE INFO

Keywords:
Nosology
Leonhard
Follow-up
First-episode psychosis
Cycloid
Schizophrenia

ABSTRACT

The validation of nosological diagnoses in psychiatry remains a conundrum. Leonhard's (1979) nosology seems to be one of the few acceptable alternative categorical models to current *DSM/ICD* systems.

We aimed to empirically validate Leonhard's four classes of psychoses: systematic schizophrenia (SSch), unsystematic (USch), cycloid psychosis (Cyclo), and manic-depressive illness (MDI) using a comprehensive set of explanatory validators.

243 patients with first-episode psychosis were followed between 10 and 31 years. A wide-ranging assessment was carried out by collecting data on antecedent, illness-related, concurrent, response to treatment, neuromotor abnormalities, and cognitive impairment variables.

Compared with USch, Cyclo, and MDI, SSch displayed a pattern of impairments significantly larger across the seven blocks of explanatory variables. There were no significant differences between Cyclo and MDI in explanatory variables. Except for the majority of illness-onset features, USch displayed more substantial abnormalities in the explanatory variables than Cyclo and MDI. SSch and MDI showed higher percentages of correctly classified patients than USch and Cyclo in linear discriminant analyses.

Partial validation of Leonhard's classification was found. SSch showed differences in explanatory variables with respect to Cyclo and MDI. USch showed also significant differences in explanatory variables regarding Cyclo and MDI, although with a lower strength than SSch. There was strong empirical evidence of the separation between both Leonhard's schizophrenia subtypes; however, the distinction between the Cyclo and MDI groups was not empirically supported. A mild to moderate discriminative ability between Leonhard's subtypes on the basis of explanatory blocks of variables was observed.

1. Introduction

Current nosological systems for diagnosing psychoses are continuously updated by advances in research, and they play an indispensable role in psychiatrists' daily practice. However, the long-sought goal of these classifications to identify the neurobiological basis of psychosis has not yet been achieved despite extensive research over the past few centuries (Kapur et al., 2012).

Dimensional proposals and new systematics (Kotov et al., 2017; Insel et al., 2010) have been proposed as alternatives to categorically defined disorders in psychosis to characterise new phenotypes to be tested in the biomedical paradigm (APA, 2013; WHO, 2019). However, very few alternative nosological systems to categorical classifications have been proposed. The most outstanding psychopathological system was developed proposed by Leonhard (Leonhard, 1979; Ungvari, 1993). Leonhard's (1979) subtypes of endogenous psychoses were mainly founded

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https://doi.org/10.1016/j.schres.2022.12.022
Received 13 October 2022; Received in revised form 21 December 2022; Accepted 22 December 2022

on the basis of symptomatic complexes, catamnesis-related outcomes, and genetic background, within a model of 'brain diseases' (Foucher et al., 2020; Leonhard, 1979).

According to Leonhard's nosology, there are four main types of disease processes: systematic schizophrenia, bipolar unsystematic schizophrenia, bipolar cycloid psychosis, and phasic psychosis that includes manic-depressive illness and monopolar affective psychoses (Astrup and Fish, 1964; Ban, 1982; Ban et al., 1984; Leonhard, 1979; Stober et al., 1997). In addition, Leonhard differentiated 35 subtypes within these four general classes of endogenous psychoses (Foucher et al., 2020; Leonhard, 1979; Peralta et al., 2016; Ungvári, 1985). Recently, Foucher et al. (2020) made an outstanding contribution to Leonhard's nosology by reporting good reliability and predictive, face, construct, and differential validity of their 35 major phenotypes based on lifelong diachronic observations.

First-episode psychosis (FEP) shows a marked heterogeneity in course and outcome both in the short and long term (García de Jalón et al., 2022; Robinson et al., 1999). In this regard, the examination of the long-term outcome of a FEP sample is a window of opportunity for the clinical validation of phenotypes within endogenous psychosis.

There is no gold standard for comparing competing nosologies in psychiatry, and there still is no consensus about potential explanatory variables. Moreover, validators are heterogeneous; differ from one another; and their evidence is derived mainly from observational, not experimental, sources. In this study, we focused on aggregate validators, such as the ones being used in the steering committee for revisions of *DSM–5* (Appelbaum et al., 2021; Solomon and Kendler, 2021).

Our aim in this study was to ascertain the empirical validity of four main groups of Leonhard's psychoses in terms of a comprehensive set of explanatory validators comprising antecedent, illness-related, concurrent, response-to-treatment, neuromotor abnormalities and cognitive impairment variables.

2. Material and methods

2.1. Sample

This study was carried out on the SEGPEPS cohort (Peralta et al., 2021)., which is a long-term, follow-up, naturalistic study of FEP patients who had their first hospital admission for psychosis between January 1990 and December 2008.

The inclusion criteria for participants were a diagnosis of FEP meeting *DSM–III–R* (APA, 1987) or *DSM–IV* (APA, 1994) criteria, between ages 15 and 65, living in the hospital's catchment area, finishing the inpatient treatment period and undergoing a 6-month assessment after discharge, having close relatives available to provide background information, and giving written informed consent. Exclusion criteria included having taken antipsychotic medication in the past for >2 months, a drug-induced psychosis diagnosis that was either suspected or confirmed, a history of a major medical condition or neurological disorder, and an IQ <70.

Between January 2018 and May 2021, FEP patients were tracked to evaluate the clinical trajectory and explanatory variables at a long-term follow-up; 243 patients achieved complete examinations. The *DSM–5* criteria diagnoses (APA, 2013) are displayed in Table 1.

The clinical research ethical committee of Navarra (1971/2016) gave its approval to all procedures involving patients. All procedures used in this research were in agreement with the 2008 revision of the 1975 Helsinki Declaration as well as the ethical guidelines of the national and institutional committees on human experimentation.

2.2. Assessments

Patients were assessed with the Comprehensive Assessment of Symptoms and History (CASH) semistructured interview (Andreasen, 1992). Diagnoses according with Leonhard's nosology were established by a consensus between the two senior researchers (VPM and MJC) following the Leonhard's symptom catalogue (Leonhard, 1990) together with auxiliary criteria (Table 1). All available sources of information were used, including CASH interviews and information from close relatives and ward records.

At the outset of the study, the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were scored by the CASH (Andreasen, 1992); and the level of functioning was measured by the Social and Occupational Functioning Assessment Scale (Goldman et al., 1992).

2.2.1. Antecedent explanatory variables

Polygenic risk scores (PRSs) for schizophrenia, bipolar disorder, and major depressive disorder using genome-wide genotyping were

Table 1
Sociodemographic and clinical characteristics at the first-episode of psychosis and final DSM 5 diagnoses of Leonhard's psychoses.

	1. Systematic schizophrenia (n = 55)		2. Unsystematic schizophrenia (n = 76)		3. Cycloid psychoses (n = 74)		4. Manic-depressive illness (n = 38)		ANOVA/Chi-square		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	Post-hoc
Age at follow-up	48.91	11.40	47.82	9.74	49.07	10.19	50.84	12.73	0.674	.569	ns
Illness duration (years)	25.34	6.99	22.47	6.34	22.27	7.06	20.92	7.11	3.647	.013	1 > 4
Gender men/women (n)[a]	34/21		46/30		44/30		13/25		9.702	.028	2 > 4[b]
Socioeconomic status score (1–5) at intake	3.29	0.76	3.05	0.74	2.93	0.70	3.03	0.59	2.710	.046	ns
Education, years	9.89	2.90	11.29	3.47	12.04	3.41	11.47	3.28	4.566	.004	1 < 3
SAPS total at FEP	9.98	3.83	10.29	4.14	9.57	3.76	7.53	4.41	4.302	.006	1 > 4 2 > 4
SANS total at FEP	7.85	5.32	4.50	5.23	3.85	4.84	3.87	4.43	8.104	.001	1 > 2, 3, 4
SOFAS total at FEP	66.49	18.57	79.22	16.29	87.28	12.33	85.74	13.21	21.651	.001	1 < 2, 3, 4 2 < 3, 4
DSM 5 diagnoses (n)[a]									291.657	.001	
Schizophrenia	53		50		10		0				
Schizophreniform disorder	0		0		6		0				
Brief psychotic disorder	0		0		20		0				
Delusional disorder	2		1		1		0				
Schizoaffective disorder	0		24		14		1				
Bipolar disorder/mania	0		0		14		28				
Major depressive disorder	0		0		2		8				
Psychotic disorder not otherwise specified	0		1		7		1				

[a] Chi-square statistic.
[b] USch greater male rate than MDI (post-hoc chi square).

computed using DNA samples collected at the follow-up from 164 patients. DNA samples were genotyped using the Illumina Global Screening Array, as reported elsewhere (Cuesta et al., unpublished results).

We used the Family History–Research Diagnostic Criteria (Andreasen et al., 1977) to collect the family history of schizophrenia spectrum disorders. We also evaluated obstetric complications by means of the Lewis–Murray scale (Lewis and Murray, 1987) and age when neurodevelopmental milestones were reached (Shapiro et al., 1990). The modified Gittelman–Klein scale, which is included in the CASH (Andreasen, 1992) was used to evaluate the premorbid adjustment during childhood and adolescence. We assessed childhood adversity with the Global Family Environment Scale (Rey et al., 1997), which rates the global quality of the family environment during childhood. All the antecedent measures were completed with information supplied by close relatives.

2.2.2. Illness-onset explanatory variables

Age at illness onset was defined as the age at which each participant had the FEP. We assessed duration of untreated illness (DUI) and duration of untreated psychosis (DUP) using the Symptom Onset in Schizophrenia inventory (Perkins et al., 2000). Mode of onset of FEP was rated as acute (<1 month); subacute (1–2 months); subchronic (2 to 6 months); and chronic (>6 months). We used *DSM–III* Axis IV (APA, 1980) to assess acute psychosocial stressors, and substance abuse or dependence was evaluated with the CASH.

2.2.3. Concurrent explanatory variables

Lifetime dimensional scores of psychopathological dimensions were built using the global severity ratings of the SAPS and SANS scales that are included in the CASH. Five psychopathological dimensions representing the most nuclear domains of the psychotic illness were computed: (1) reality-distortion, (2) disorganization, (3) negative symptoms, (4) mania, and (5) depression (Peralta and Cuesta, 2001). The lifetime scores were performed by averaging the severity and frequency of each psychopathological dimension from the FEP to the follow-up (Peralta et al., 2021).

The World Health Organization Short Disability Assessment Schedule (DAS-S) (Janca et al., 1996) is a semistructured interview that helps clinicians assess and rate a patient's difficulties maintaining personal, occupational, familiar, and social functioning. It was validated in Spanish for patients with schizophrenia (Mas-Expósito et al., 2012).

2.2.4. Response to treatment explanatory variables

The Clinical Global Impression Severity scale (Guy, 1976b) was used to quantify and track patient progress and treatment response over time. Lifetime scores on this instrument and the DAS-S were computed by averaging the severity and frequency of domain of functioning and response to treatment during the follow-up period (Peralta et al., 2021).

We chose two other groups of variables for assessing response to treatment: (1) the number of episodes over the follow-up and the number of episodes for consecutive periods of 2 or 5 years; (2) the average dose-years load of psychopharmacological drugs (antipsychotics, anticholinergics, stabilising and antidepressant drugs) (Andreasen et al., 2010) and the number of electroconvulsive treatments (ECTs) received.

2.2.5. Neuromotor and neurocognitive explanatory variables

Neuromotor and neuropsychological assessments were carried out by two trained psychiatrists (EGJ and LMI) who were blinded to the participants' Leonhard's diagnoses. Neuromotor and neurocognitive assessment took place at the time of the follow-up. Parkinsonism and dyskinesia were rated using the Simpson–Angus Rating Scale (Simpson and Angus, 1970) and the Abnormal Involuntary Movement Scale (Guy, 1976a, 1976b), respectively. The Neurological Examination Schedule (Buchanan and Heinrichs, 1989), to assess neurological soft signs, and the Modified Rogers Scale, to assess symptoms of catatonia (Lund et al., 1991) were included to capture a comprehensive assessment of neuromotor domain.

The Word Accentuation Test, which is the Spanish equivalent of the National Adult Reading Test, was used as an estimate of premorbid IQ (Gomar et al., 2011). Neuropsychological assessment done by means of the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) that assess seven different cognitive functions: attention/vigilance, processing speed, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. Two trained neuropsychologists administered the battery in a single session (AST and GGB). Scores are recorded with corrected values for age and education and normalised values (T scores). One hundred seventy-two patients completed the neuropsychological assessments.

2.3. Statistical analyses

We used univariate analyses to examine, at the follow-up, the differences in sociodemographic, psychopathological, illness-related, treatment, and functioning variables between patients who abandoned and those who completed the study, by means of independent *t*-tests.

We used analyses of variance and χ^2 statistics for the examination between groups. We conducted Scheffé post hoc tests in the analyses of variance and pairwise *Z* test in the χ^2 independence tests to estimate all possible contrasts between groups.

Independent linear discriminant function analyses (LDFA) using the Wilks's λ method were performed to examine the percentages of correct classification of the four Leonhard groups of endogenous psychoses on the basis of the seven blocks of validators. We entered separately the seven blocks of validators, including in each block only the resulting significant variables in univariate analyses. The seven blocks of explanatory variables were (1) antecedent, (2) illness-onset features, (3) lifetime psychopathological dimensions, (4) lifetime functioning, (5) response to treatment, (6) neuromotor abnormalities, and (7) cognitive impairment.

All analyses were conducted using IBM SPSS Statistics (Version 26) and were two tailed with a critical p value of .05, except where noted.

3. Results

Our original FEP cohort included 510 patients, but after the long follow-up (20.3 ± 5.6 years) the final cohort examined included 243 (47.6 %). No significant differences were found between final-examined patients and those lost during the follow-up in baseline demographic (age and gender), global psychopathology (SAPS and SANS global scores), global functioning (Social and Occupational Functioning Assessment Scale score, SOFAS) (Morosini et al., 2000), and baseline *DSM–5* diagnoses.

At the follow-up examination the patients' average age was 48.1 ± 10.7, and 51.7 % were male. The diagnoses of Leonhard's classification were as follows: systematic schizophrenia (SSch; n = 55, 22.6 %), unsystematic schizophrenia (USch; n = 76, 31.3 %), cycloid psychosis (Cyclo; n = 74, 30.5 %), and manic-depressive illness (MDI; n = 38, 15.6 %; see Table 1).

There were no significant differences among the four psychosis groups in terms of age at follow-up and socioeconomic level. SSch showed a significant longer duration of illness than MDI, USch had a higher rate of males than MDI, and SSch had a lower educational level than Cyclo. *DSM–5* diagnoses showed strong significant differences across subgroups (Table 1). SSch had higher SAPS scores than MDI at study intake, and they had higher SANS scores and poorer functioning than USch, Cyclo, and MDI. Likewise, USch showed poorer functioning than Cyclo and MDI.

3.1. Antecedent validators

There were no differences in regard to the polygenic risk scores for schizophrenia, bipolar disorder, and major depressive disorder among the four groups. A positive family history of schizophrenia, but not of bipolar disorder or major depression, revealed significant differences among the four groups and was particularly higher in SSch regarding MDI. SSch showed significantly more obstetric complications, neurodevelopmental abnormalities, and childhood adversity than the three remaining groups, and they had experienced poorer childhood and adolescence adjustment (Table 2). USch showed higher neurodevelopment abnormalities and childhood adversity than Cyclo and poorer childhood and adolescence adjustment than Cyclo and MDI (Table 2).

3.2. Illness-onset features

SSch showed significantly higher DUP and DUI than the three remaining groups and an earlier onset of illness than MDI. An acute mode of onset was significantly less frequent in SSch than in USch, Cyclo, and MDI (Table 2). There were no significant differences in premorbid drug abuse among the four groups. Cyclo showed more often had acute psychosocial stressors compared with SSch, USch, and MDI (see Table 2).

3.3. Concurrent validators

When we profiled psychopathological dimensions over the entire course of illness (lifetime dimensions), we noted that SSch had significantly higher levels of reality distortion and negative dimensions, and lower mania, than the USch, Cyclo, and MDI. In addition, USch had higher levels of reality distortion and negative dimensions than the Cyclo and MDI. Also, SSch had lower lifetime scores in depression, but higher catatonia, than MDI (see Table 3).

Regarding lifetime psychosocial functioning, SSch developed significantly poorer personal, occupational, familiar, social, and global functioning than USch, Cyclo, and MDI; and USch had poorer functioning than Cyclo and MDI (Table 3).

3.4. Response to treatment validators

SSch patients had a higher lifetime clinical global impression over the entire course of illness than the USch, Cyclo, and MDI groups. However, there were no significant differences in the number of episodes across groups when the course was broken into short periods of years (Table 3). There were no significant differences among groups in either the number of total episodes or in the number of episodes after the first year and later years of the FEP (Table 3).

Regarding the predominant pharmacological treatment received during the whole illness course, both schizophrenia subtype groups received higher doses of antipsychotic drugs than Cyclo and MDI, but there were no differences between them (SSch and USch). USch received a higher load of anticholinergic drugs than Cyclo. SSch received lower doses of stabilising drugs than USch, Cyclo, and MDI, and USch received lower doses than Cyclo and MDI.

There were no significant differences across the diagnostic groups in the load of antidepressant drugs and the number of ECT sessions.

3.5. Long-term neuromotor and neurocognitive outcomes

Parkinsonism and catatonia were significantly higher in the long-term assessments of SSch compared with USch, Cyclo, and MDI, and in dyskinesia compared with Cyclo and MDI. USch showed higher catatonia scores than Cyclo (see Table 4). Neurological soft signs were

Table 2
Antecedent and 'illness-onset features' validators of Leonhard's psychoses.

	1. Systematic schizophrenia (n = 55)		2. Unsystematic schizophrenia (n = 76)		3. Cycloid psychoses (n = 74)		4. Manic-depressive illness (n = 38)		ANOVA/Chi-square		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	Post-hoc
Antecedents											
Polygenic risk scores (n = 164)											
Schizophrenia	0.07	0.72	−0.03	1.10	−0.09	1.02	0.13	1.05	0.408	.704	ns
Bipolar disorder	−0.05	0.84	0.13	1.05	−0.11	1.04	−0.01	1.02	0.574	.633	ns
Major depressive disorder	0.21	0.96	0.12	0.98	−0.29	0.95	−0.01	1.06	2.21	.089	ns
Familial history (present = 0/absent = 1)											
SZ-FH	0.33	0.47	0.24	0.42	0.15	0.35	0.05	0.22	4.324	.005	1 > 4
BIP-FH	0.04	0.18	0.08	0.27	0.11	0.31	0.13	0.34	1.070	.182	ns
MDD-FH	0.13	0.36	0.09	0.29	0.22	0.41	0.21	0.41	1.874	.135	ns
Obstetric complications	0.62	0.75	0.16	0.43	0.11	0.39	0.03	0.16	15.817	.000	1 > 2, 3, 4
Neurodevelop. score	2.24	1.77	0.99	1.28	0.42	0.77	0.32	0.66	28.616	.000	1 > 2, 3, 4 2 > 3
Childhood Adversity	50.11	19.57	68.93	22.67	81.35	12.70	78.58	16.50	33.564	.000	1 < 2, 3, 4 2 < 3
Childhood adjustment	4.04	2.26	2.49	1.71	1.57	1.36	1.24	1.32	28.476	.000	1 > 2, 3, 4 2 > 3, 4
Adolescence adjustment	5.16	2.29	3.16	2.14	1.86	1.67	1.61	1.70	36.263	.000	1 > 2, 3, 4 2 > 3, 4
Illness-onset features											
Age at onset	23.78	10.21	25.21	7.90	26.34	8.92	29.84	11.08	3.417	.018	1, 2 < 3, 4[b]
Mode of onset (n)[a] (acute, subacute, subchronic, chronic)	4/4/6/41		15/15/13/33		30/21/14/9		17/17/1/5		77.100	.001	
DUI (months)	40.58	57.24	15.71	25.73	12.97	50.82	10.42	20.72	5.879	.001	1 > 2,3, 4
DUP (months)	29.18	49.94	6.71	14.05	1.34	1.68	1.17	1.16	15.655	.001	1 > 2,3, 4
Drug abuse[a] (n) (present/absent)	20/35		23/53		29/45		9/29		3.284	.350	ns
Acute psychosocial stressors[a] (n) (present/absent)	4/51		6/70		24/50		14/24		26.653	.001	

[a] Chi-square statistic.
[b] Greater rate of acute onset of Cyclo and MDI than SSch and USch (post-hoc chi square).

Table 3
Concurrent and response to treatment validators of Leonhard's psychoses.

	1. Systematic schizophrenia (n = 55)		2. Unsystematic schizophrenia (n = 76)		3. Cycloid psychoses (n = 74)		4. Manic-depressive illness (n = 38)		ANOVA/Chi-square		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	Post-hoc
Concurrent variables											
Lifetime psychopathological dimensions											
Reality-distortion	6.11	2.21	4.99	1.81	3.20	2.07	2.91	1.40	33.471	.000	1 > 2, 3, 4 2 > 3, 4
Negative	6.80	1.92	4.95	2.20	1.77	2.11	2.11	2.17	74.927	.000	1 > 2, 3, 4 2 > 3, 4
Disorganization	3.90	2.95	3.50	2.35	1.82	1.84	2.23	1.77	11.750	.000	1 > 3, 4
Mania	0.71	1.19	1.70	2.02	1.65	2.04	2.59	2.02	7.717	.000	1 < 2, 3, 4
Depression	2.21	2.02	2.82	2.18	2.05	1.90	3.42	1.91	4.825	.003	1 < 4
Lifetime functioning domains											
DAS-S personal	1.82	1.38	1.26	1.09	0.33	0.68	0.40	0.73	28.593	.000	1 > 2, 3, 4 2 > 3, 4
DAS-S occupational	3.32	1.21	2.45	1.20	0.79	1.14	1.22	1.43	53.497	.000	1 > 2, 3, 4 2 > 3, 4
DAS-S familiar	2.39	1.10	1.57	1.33	0.47	0.82	0.73	0.99	37.506	.000	1 > 2, 3, 4 2 > 3, 4
DAS-S social	3.14	1.03	2.14	1.15	0.77	0.88	0.86	0.97	69.825	.000	1 > 2, 3, 4 2 > 3, 4
DAS-S total	11.20	4.13	8.73	4.39	2.86	3.56	3.21	3.85	61.643	.000	1 > 2, 3, 4 2 > 3, 4
Response to treatment											
Clinical Global Impression-Severity scale (CGI-S) (maximum severity lifetime)	6.24	0.88	5.34	1.48	4.62	1.46	4.50	1.30	19.356	.000	1 > 2, 3, 4 2 > 3, 4
Number of episodes											
0–2 years	2.05	2.11	1.88	1.25	1.58	0.74	1.61	0.67	1.726	.162	ns
3–5 years	1.64	2.55	1.76	1.67	1.27	1.73	1.39	1.65	0.941	.422	ns
5–10 years	2.42	5.57	2.21	2.54	1.34	1.85	1.66	1.82	1.500	.215	ns
11–15 years	1.54	2.25	1.69	1.97	1.24	1.83	1.16	1.21	0.863	.461	ns
16–20 years	0.89	1.45	1.49	1.37	1.18	1.72	1.50	2.54	1.009	.391	ns
>21 years	0.49	1.30	1.03	1.45	0.80	1.95	0.89	2.07	1.091	.354	ns
Number of episodes (total)	10.38	15.17	10.84	6.93	8.20	8.22	9,31	6.59	0.608	.611	ns
Dose-years drugs											
Antipsychotic	83.07	44.45	63.97	41.50	41.50	44.47	22.68	21.74	20.553	.000	1 > 3, 4 2 > 3, 4
Anticholinergic	17.11	25.56	18.41	29.98	7.06	21.67	5.43	14.12	4.363	.005	2 > 3
Stabilising	6.30	14.76	26.88	35.86	29.18	40.75	41.24	35.63	8.874	.000	1 < 2, 3, 4 2 < 3, 4
Benzodiazepine	44.93	44.65	34.62	35.77	17.28	26.17	20.91	28.53	8.128	.000	1 > 3, 4 2 > 3
Antidepressant	26.25	37.33	28.12	39.19	20.98	30.07	35.03	41.80	1.296	.277	ns
ECT (number)	0.85	3.30	2.86	13.74	3.64	11.57	5.11	16.74	1.034	.378	ns

significantly higher in SSch compared with Cyclo and MDI and in USch compared with Cyclo. There were no significant differences between the SSch and USch (Table 4).

Lower significant premorbid IQ was found in the SSch group. There were no significant differences in cognitive domain and global scores on the MCCB between the SSch and USch. SSch significantly underperformed in verbal memory with respect to Cyclo and MDI, in attention and global cognition compared with Cyclo, and in processing speed compared with MDI. Significantly lower processing speed was evidenced in the USch group compared with Cyclo (Table 4).

3.6. Linear discriminant analysis models

The SSch group had a high proportion of correctly classified patients (>60 %) in five blocks of validators (antecedent, lifetime psychopathological dimensions, lifetime functioning, response to treatment, and cognitive impairment). The MDI group had >50 % of correctly classified patients in four blocks of validators (antecedent, lifetime psychopathological dimensions, and cognitive impairment). The Cyclo group had >50 % in three blocks (lifetime psychopathological dimensions, lifetime functioning, and neuromotor abnormalities), and the USch group showed only >50 % of patients correctly classified in the block of lifetime psychopathological dimensions (see Fig. 1 and Table 5). All models obtained significant Wilks's λs.

4. Discussion

This study examined the clinical validation of the four main groups

Table 4
Long-term neuromotor and neurocognitive outcomes of Leonhard's psychoses.

	1. Systematic schizophrenia (n = 55)		2. Unsystematic schizophrenia (n = 76)		3. Cycloid psychoses (n = 74)		4 Manic-depressive illness (n = 38)		ANOVA/Chi-square		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	Post-hoc
Neuromotor outcomes											
Parkinsonism	6.69	6.82	4.78	4.72	2.66	3.53	3.21	4.06	8.022	.000	1 > 2, 3, 4
Akathisia	0.49	0.97	0.46	0.85	0.15	0.45	0.11	0.38	4.390	.005	ns
Dyskinesia	1.89	3.45	1.33	2.50	0.38	0.93	0.45	1.35	5.889	.001	1 > 3, 4
Catatonia	12.25	13.99	7.42	9.40	2.97	4.10	4.34	6.52	11.843	.000	1 > 2, 3, 4 2 > 3
Neurological soft-signs	26.51	15.14	20.79	10.77	13.65	9.38	19.00	12.37	11.521	.000	1 > 3, 4 2 > 3
Neurocognitive outcomes											
WAT_IQ	90.44	12.65	97.91	12.21	103.09	10.70	102.63	10.36	14.400	.000	1 < 2, 3, 4
Attention/vigilance	35.00	10.99	38.50	9.51	44.84	10.57	41.30	9.67	6.064	.001	1 < 3
Processing speed	30.00	15.02	34.26	11.56	37.21	12.71	38.75	8.80	3.365	.020	1 < 4 2 < 3
Working memory	36.45	13.87	38.66	12.02	43.27	12.27	42.78	10.71	2.782	.043	
Verbal memory	29.55	18.66	32.42	12.88	39.63	15.64	40.47	15.51	4.687	.004	1 < 3, 4
Visual memory	34.06	17.51	34.59	14.93	41.44	14.90	39.69	12.51	2.626	.052	ns
Executive function	35.57	11.69	36.69	10.20	39.69	11.03	36.66	9.85	1.174	.321	ns
Social cognition	39.59	12.88	43.45	11.36	47.00	12.30	50.19	8.15	5.224	.002	1 < 4
Global cognition	28.50	15.23	31.58	12.88	38.40	13.93	37.70	9.75	4.526	.005	1 < 3

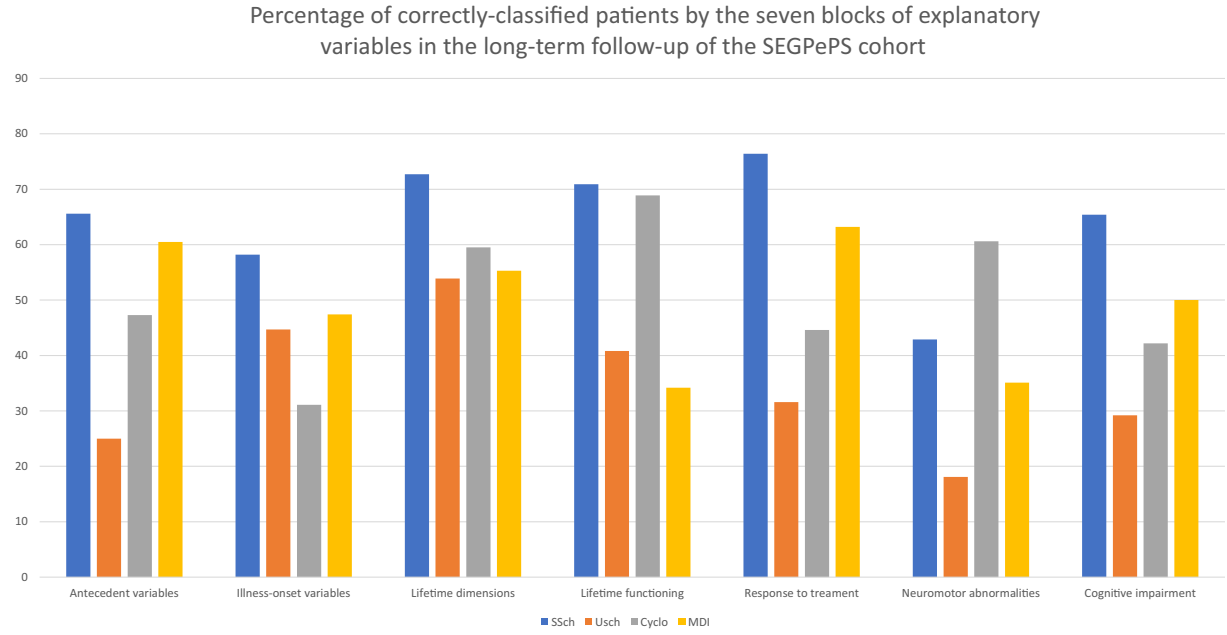

Fig. 1. Percentage of correctly-classified patients by the seven blocks of explanatory variables in the long-term follow-up of the SEGPePS cohort.

of psychoses according to Leonhard's nosology in a long-term follow-up of FEP patients. Four main conclusions were drawn from this study. First, SSch showed a pattern of significantly higher abnormalities or impairments in the seven groups of explanatory variables compared with USch, Cyclo, and MDI. Second, no significant differences between Cyclo and MDI in any explanatory variable were found. Third, USch showed significant abnormalities in the explanatory variable groups compared with Cyclo and MDI, except for most illness-onset features. Fourth, SSch and MDI showed higher percentages of correctly classified patients than USch and Cyclo in linear multiple discriminant analyses after we entered the seven blocks of explanatory variables.

We applied, for the first time, both PRS methodology and a family history method to compare the four groups of Leonhard's classification. Our study failed to find significant differences among the four groups in the three PRSs (for schizophrenia, bipolar disorder, and major depressive disorder). However, caution is warranted in the interpretation of PRS results because they are still very limited to use in clinical practice for helping in differential diagnoses across the psychosis spectrum (Fusar-Poli et al., 2022; Trubetskoy et al., 2022). Genetic studies of USch have reported high estimates of heritability for only one of its subtypes (periodic catatonia) (Krüger and Bräunig, 1995; Leonhard, 1979), which is an infrequent disease, but this does not extend to the whole USch group (Peralta et al., 2016). To gain a deeper insight into antecedents, we also analysed the family history of our patients. Our results are in partial agreement with our previous ones (Peralta et al., 2016) because we found more family antecedents of schizophrenia in SSch than in MDI, but we did not find significant differences in the family antecedents of bipolar disorder and major depression among the groups. In addition, we could not replicate Leonhard's findings regarding differences in heritability between USch subtypes (high

Table 5
Linear discriminant analyses (% correctly classified) of Leonhard's system of endogenous psychosis by blocks of validators (antecedent, illness-onset, lifetime psychopathological dimensions, lifetime functioning, response to treatment, neurological abnormalities and cognitive impairment).

	SSch	Usch	Cyclo	MDI	Total % of correct classified
Antecedent variables					**46.5**
SZ-FH; obstetric	**65.5**	21.8	3.6	9.1	
complications;	23.7	**25.0**	32.9	18.4	
neurodevelopment. score;	1.4	16.2	**47.3**	35.1	
childhood adversity;	2.6	13.2	23.7	**60.5**	
childhood and adolescence premorbid adjustment					
Illness-onset features					**44.0**
Age at onset; mode of onset	**58.2**	27.3	5.5	9.1	
(acute); DUI (months); DUP	22.4	**44.7**	18.4	14.5	
(months); drug abuse and	5.4	21.6	**31.1**	41.9	
acute psychosocial stressors	0.0	21.1	31.6	**47.4**	
(no/yes)					
Lifetime psychopathological dimensions					**60.1**
Reality-distortion; negative;	**72.7**	25.5	0.0	1.8	
disorganization; mania;	23.7	**53.9**	9.2	13.2	
depression	2.7	18.9	**59.5**	18.9	
	0.0	10.5	34.2	**55.3**	
Lifetime functioning					**55.1**
DAS-S personal, occupational,	**70.9**	18.2	3.6	7.3	
familiar, social and total	27.6	**40.8**	18.4	13.2	
	6.8	10.8	**68.9**	13.5	
	7.9	13.2	44.7	**34.2**	
Response to treatment					**50.6**
Lifetime CGI-S score; total	**76.4**	16.4	3.6	3.6	
number of admissions; dose-	30.3	**31.6**	21.1	17.1	
years of antipsychotic,	9.5	21.6	**44.6**	24.3	
anticholinergic, stabilising	5.3	2.6	28.9	**63.2**	
and benzodiazepine drugs					
Neuromotor abnormalities					**38.8**
Parkinsonism; dyskinesia;	**42.9**	8.2	22.4	26.5	
catatonia and neurological	27.8	**18.1**	34.7	19.4	
soft-signs	9.1	7.6	**60.6**	22.7	
	13.5	5.4	45.9	**35.1**	
Cognitive impairment					**43.6**
WAT_IQ; attention; processing	**65.4**	15.4	7.7	11.5	
speed; working memory;	29.2	**29.2**	22.9	18.8	
verbal memory; social	17.8	11.1	**42.2**	28.9	
cognition; global cognition	6.7	20.0	23.3	**50.0**	

heritability for periodic catatonia) because the low prevalence of subtypes with predominant catatonic symptoms. Only 7 patients were diagnosed of periodic catatonia in the USch group (9.21 %) and 12 as catatonic schizophrenia in the SSch group (21.8 %), such as it was reported in other studies (Franzek and Beckmann, 1998; Stober et al., 1995). Moreover, 12 patients received a diagnosis of motility psychosis in the Cyclo group (22.9 %) and 8 patients showed predominant catatonic symptoms in affective psychosis group (13.1 %).

SSch and USch patients showed greater abnormalities from childbirth to adult life antecedents than did Cyclo and MDI patients, including obstetric complications, neurodevelopment delay, unstable childhood, and adolescence adjustment. Moreover, they experienced poorer family environments. Our results cannot be compared with others in the literature because most studies of Leonhard's nosology have been focused on the course of a psychosis but not the antecedents. However, Stober et al.'s (1993) study of SSch and USch patients and did not find significant differences in OCs between the groups.

In this study, Cyclo patients showed significantly higher proportions of acute onset than the remaining groups. This is in agreement with Leonhard's (Leonhard, 1965, 1990) seminal proposals, and acute onset is even included in diagnostic criteria of Cyclo (El-Mallakh and Furdek, 2018; Perris and Brockington, 1981). Age at onset was significantly lower, and DUP and DUI longer, in SSch, which is in agreement with the associations between longer DUP and DUI in schizophrenia and worse overall treatment outcomes sustained throughout the 20 years (Cechnicki et al., 2014). Acute psychosocial stressors were higher for MDI and Cyclo than both SSch and USch, as has been reported in previous articles (Leonhard, 1965; Pfuhlmann et al., 2004).

Increased lifetime severity and persistence of psychopathological dimensions were characteristic of both schizophrenia groups over the long-term follow-up. This finding is in agreement with the longitudinal trajectory of symptom complexes described in Leonhard's nosology. Moreover, and in agreement with the pioneering proposals of Leonhard (1979), USch patients did not show a long-term outcome as poor as that of SSch but revealed a singularly poorer outcome than Cyclo and MDI (Fish, 1958; Leonhard, 1979). These results are in agreement with our findings of greater severity in the clinical global impression (lifetime measure) for SSch and USch compared with Cyclo and MDI. However, one would expect that Cyclo psychoses, that are highly polymorphic and recurrent, have more global episodes or more recurrences close to the FEP (Leonhard, 1965). But unexpectedly, we did not find differences over the short or long term in the number of psychotic episodes among the four groups.

In observational studies conducted before the development of newer antipsychotic drugs (Astrup and Fish, 1964; Ban, 1990; Fish, 1964), USch responded considerably better to neuroleptic drugs than SSch. We estimated indirectly patients' response to treatment assuming that the higher accumulative doses might be associated with patients who are more refractory (i.e., prone to relapse). Both schizophrenia groups received higher doses of antipsychotic and benzodiazepine drugs. USch received higher doses of anticholinergic drugs than Cyclo and MDI, and Cyclo and MDI received higher doses of stabilising drugs than both schizophrenia groups, but USch had higher levels than SSCh, which is in full agreement with the bipolar profile of USch, Cyclo, and MDI suggested by Leonhard (1979, 1990). Moreover, because cycloid psychoses by definition have a favourable short-term outcome they do not need antipsychotic long-term treatment (Leonhard and Beckmann, 2003).

Numerous case reports have indicated a quick and beneficial effect of ECT for Cyclo, but drug therapy is also effective (El-Mallakh and Furdek, 2018; Holm et al., 2017). ECT is very effective for catatonia and the periodic catatonia subphenotype of USch (Leonhard, 1999; Pelzer et al., 2018; Walther et al., 2019), but less evidence has been reported in regard to SSch. However, in our study there were no significant differences in the number of ECTs received over time among groups.

Leonhard (1990) considered that motor symptoms were mainly focused on catatonic symptoms and included it in the descriptions of subtypes of his classification. However, other neuromotor domains were not considered and no previous studies addressed this topic. In our study, SSch showed higher long-term catatonia scores than USch, Cyclo, and MDI, and USch had higher scores than Cyclo but not MDI. In addition, SSch showed higher long-term scores on parkinsonism and neurological soft signs than did USch, Cyclo, and MDI and higher dyskinesia scores than Cyclo and MDI. USch had higher soft signs scores than Cyclo.

Neuropsychological studies of Leonhard's subtypes are scarce and mainly address only some of the subtypes. Our results are in agreement with a previous cross-sectional study of our group (Cuesta et al., 2022) that found that premorbid cognitive achievement was significantly lower in SSch compared with the other three groups. In general, SSch showed the greatest cognitive impairment, USch showed an intermediate performance, and Cyclo and MDI were the least impaired in cognitive domains. SSch showed greater impairment in verbal memory than Cyclo and MDI. Moreover, SSch scored lower on measures of attention and global cognition compared with Cyclo and lower on measures of processing speed than MDI. USch showed great impairment in processing speed compared with Cyclo.

The four groups of Leonhard's endogenous psychoses achieved low to moderate rates of classifications in the LDFA of blocks of explanatory variables (between 38 % and 60 %), with SSch being the best

discriminated subtype, MDI and Cyclo intermediate, and USch being the least discriminated. Lifetime psychopathological and functioning dimensions and response to treatment showed rates of correctly classified diagnoses between 50 % and 60 %. There are very few studies that have addressed the discriminative power of categories in psychoses (Brockington et al., 1991; Taylor and Amir, 1994). Our results are in partial agreement with those of Brockington et al. (1991), who reported that the category of bipolar illness, as defined by *DSM–III*, identified a group that was clearly distinct from the rest of psychotic illness but, in the group of schizophrenia diagnoses, was not well defined because an excess of intermediate cases. Our patients with MDI probably were similar to those with *DSM–III* bipolar disorder in Brockington et al.'s study, but a *DSM–III* schizophrenia diagnosis probably included our SSch and USch groups, reducing the rates of correct classification.

In this article, we have reported a partial validation of Leonhard's classification of endogenous psychoses. Mild to moderate discriminative ability among the four groups of Leonhard's psychoses was observed on the basis of explanatory variables. However, both of Leonhard's schizophrenia subtypes showed significant differences in explanatory variables with respect to Cyclo and MDI, although the differences were less pronounced for USch than for SSch. Moreover, there was strong empirical evidence of the separation between both of Leonhard's schizophrenia subtypes. Finally, the distinction between the Cyclo and MDI groups was not empirically supported, so we suggest they are part of the same group.

Role of the funding source

This work was supported by the Government of Navarra (grants 17/31 and 18/41) and by the Carlos III Health Institute (FEDER Funds) from the Spanish Ministry of Economy and Competitiveness (16/2148 and 19/1698).

CRediT authorship contribution statement

MJ Cuesta and V Peralta designed the study and supervised the draft completion. AM Sánchez-Torres, GJ Gil-Berrozpe, E García de Jalón and L Moreno-Izco collected the cognitive and clinical data, managed the literature searches and contributed to the data analyses. A Zarzuela contributed to data analyses and draft completion. L Fañanás and S Papiol managed the biological samples and performed the PRS scores analyses. Authors included in SEGPEPs contributed to participants' recruitment and to the clinical assessments. MJ Cuesta wrote the first draft of the manuscript. All authors contributed to and approved the final draft of the manuscript.

Conflict of interest

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgements

We thank all the subjects for their participation in the study.

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