

Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: a review of their validity

Jack R. Foucher, MD, PhD; Micha Gawlik, MD; Julian N. Roth, MD; Clément de Crespin de Billy, MD; Ludovic C. Jeanjean, MD, MNeuroSci; Alexandre Obrecht, MPsych; Olivier Mainberger, MD; Julie M. E. Clauss, MD, MPhilSt; Julien Elowe, MD; Sébastien Weibel, MD, PhD; Benoit Schorr, MD, MNeuroSci; Marcelo Cetkovich, MD; Carlos Morra, MD; Federico Rebok, MD; Thomas A. Ban, MD; Barbara Bollmann, MD; Mathilde M. Roser, MD; Markus S. Hanke, MD; Burkhard E. Jabs, MD; Ernst J. Franzek, MD; Fabrice Berna, MD, PhD; Bruno Pfuhlmann, MD

While the *ICD-DSM* paradigm has been a major advance in clinical psychiatry, its usefulness for biological psychiatry is debated. By defining consensus-based disorders rather than empirically driven phenotypes, consensus classifications were not an implementation of the biomedical paradigm. In the field of endogenous psychoses, the Wernicke-Kleist-Leonhard (WKL) pathway has optimized the descriptions of 35 major phenotypes using common medical heuristics on lifelong diachronic observations. Regarding their construct validity, WKL phenotypes have good reliability and predictive and face validity. WKL phenotypes come with remarkable evidence for differential validity on age of onset, familiarity, pregnancy complications, precipitating factors, and treatment response. Most impressive is the replicated separation of high- and low-familiarity phenotypes. Created in the purest tradition of the biomedical paradigm, the WKL phenotypes deserve to be contrasted as credible alternatives with other approaches currently under discussion.

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Introduction

The field of endogenous psychoses is the one for which the hypothesis of “brain diseases” is the most likely in psychiatry. The past 40 years’ exclusive use of *International Classification of Diseases (ICD) – Diagnostic and Statistical Manual of Mental Disorders (DSM)* diagnoses,¹ although successful in the field of clinical psychiatry as an applied science, did not allow significant progress in biological psychiatry as a basic science. Two postulates of consensus

classifications might have made them unsuitable for this task. First, consensus criteria could not be changed, ruling out any attempt to optimize the descriptions. Second, the atheoretical stance negated any etiological or pathophysiological hypothesis,² eg, making no distinction between endogenous and neurotic depressions such as bereavement.³

The traditional *biomedical paradigm* starts from *phenotypes* rather than consensus-based *disorders*. Embracing the *naturalistic framework*,⁴ it posits that a disease is a

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - Foucher et al

natural entity defined by an *etio-pathophysiological model* which accounts for the phenotype.⁵ The model is given at the biological level, assuming a single and rare cause of major effect due to selection pressure. The typical correlation-experimental 2-step process is the theory-of-proof of the biomedical paradigm that validates the model, turning it into a *disease*. The major strength of this approach stems from this *model validity* or validity per se which translational research converts into the magic triplet of applied medicine: diagnosis, diagnostic test, and treatment.⁴

The limited construct validity of *ICD-DSM* disorders, even for schizophrenia,⁶ and the recurrent failures to validate any biological model that could account for them, raised doubt about the suitability of the biomedical paradigm in basic psychiatry.⁷ The leading proposals now turn towards dimensional approaches, which come with a major paradigmatic framework shift with the adoption of *normativistic* assumptions.^{8,9} Here a disease is defined as a *pathological deviance*, ie, a mere deviation from the norm, which makes the implicit hypothesis of multiple and frequent causes of very small effects.⁴ These are typically referred to as risk factors or modifiers in medicine rather than diseases, and translate into much less efficient interventions.⁴

Yet, consensus classifications never claimed to be fair implementations of the biomedical paradigm. They were mainly designed for clinical use and not for basic research. Hence, their lack of success in field does not rule out the relevance of the naturalistic framework in psychoses. Indeed, at least one research program, referred to as the Wernicke-Kleist-

Leonhard (WKL) pathway,¹⁰ was able to define clear-cut phenotypes. This paper gives an overview of the principles that guided their optimization,¹¹ and reviews the evidence supporting their construct validity. Validity per se will be only considered for periodic catatonia which currently has the most supported biological model. The terminology has been slightly changed relative to previous publications to adapt to current clinical psychiatry and neuroscience (*Appendix 1*).

Epistemological framework and methods

Major heuristics that guided the empirical elaboration of the phenotypes

The naturalistic assumptions state that, due to selection pressure, disabling phenotypes are accounted for by a single and rare cause of major effect. Hence, they are *categorical* in nature and liable to the *principle of parsimony*.⁴ A phenotype is a “typical” set of observable characteristics shared by a group of patients¹² which includes the *clinical presentation*, ie, the set of reported symptoms and clinical signs collected from the patient’s examination, but also the *course of the symptoms*, ie, how they appear, which ones persist, which ones disappear, or whether they completely change from one clinical picture to its opposite (bipolarity). Finally, typical *contextual elements* might also enrich the description. The WKL School *empirically* optimized their phenotype descriptions by sorting patients according to their long-term catamnestic observations following heuristics stemming from the principle of parsimony: symptom-complex, longitudinal and family-aggregation principles (*Box 1; Appendix 2*).

Author affiliations: ICube - CNRS UMR 7357, neurophysiology, FMST, University of Strasbourg, France (Jack R. Foucher, Clément de Crespin de Billy, Ludovic C. Jeanjean, Alexandre Obrecht, Olivier Mainberger); CEMNIS - Noninvasive Neuromodulation Center, University Hospital Strasbourg, France (Jack R. Foucher, Clément de Crespin de Billy, Ludovic C. Jeanjean, Alexandre Obrecht, Olivier Mainberger); Department of Psychiatry and Psychotherapy, University of Würzburg, Würzburg, Germany (Micha Gawlik, Julian N. Roth, Fabrice Berna), Pôle de Psychiatrie, Santé Mentale et Addictologie, University Hospital Strasbourg, France (Alexandre Obrecht, Julie M.E. Clauss, Sébastien Weibel, Benoit Schorr); SAGE – CNRS UMR 7363, FMST, University of Strasbourg, France (Julie M. E. Clauss); Department of Psychiatry, Prangins Psychiatric Hospital (CHUV), Route de Benex, Prangins, Switzerland (Julien Elowe, Fabrice Berna); Physiopathologie et Psychopathologie Cognitive de la Schizophrénie – INSERM 1114, FMST, University of Strasbourg, France (Sébastien Weibel, Benoit Schorr); Institute of Translational and Cognitive Neuroscience (INCYT), INECO Foundation, Favaloro University, Buenos Aires, Argentina; National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina (Marcelo Cetkovich); Sanatorio Morra, Córdoba, Argentina (Carlos Morra); “Servicio de Emergencia”, Acute Inpatient Unit, Moyano Neuropsychiatric Hospital, Buenos Aires, Argentina (Federico Rebok); International Network for the History of Neuropsychopharmacology (INH), Córdoba, Argentina (Thomas A. Ban); Klinik für Psychiatrie, Psychotherapie und Psychosomatik, Berlin, Germany (Barbara Bollmann); Department of Psychiatry, Mondor Hospital France, Creteil, France (Mathilde M. Roser); Universitäre psychiatrische Dienste Bern, Spiez, Switzerland (Markus S. Hanke); Klinik für Psychiatrie & Psychotherapie, Städtisches Klinikum Dresden, Dresden, Germany (Burkhard E. Jabs, Bruno Pfühlmann); Yes We Can Clinics, Department of Research and Development, Eindhoven, The Netherlands (Ernst J. Franzek).
Address for correspondence: Jack René Foucher, CEMNIS (UF 4768) - Centre de neuroModulation Non Invasive de Strasbourg, 1 place de l'Hôpital, BP 426, 67 091 Strasbourg Cedex, France (email: jack.foucher@gmail.com)

Principle of parsimony applied to brain, time, and family

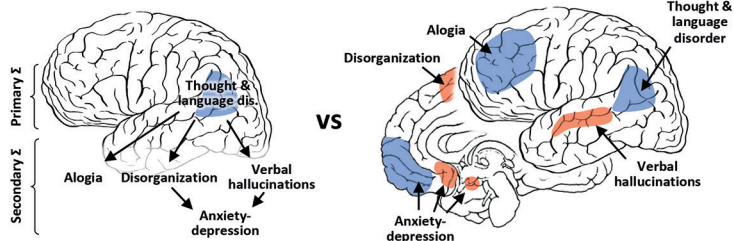
Principle of parsimony: Among competing hypotheses, the one which needs the fewest assumptions should be favored.

Hypothesizing endogenous psychoses being subtended by a **single cause of major effect** (due to selection pressure), allowed Wernicke, Kleist, and Leonhard to add the following **heuristics** to the **principle of Sydenham**, in order to define **phenotypes** and to test for their construct validity (see *Appendix 2* for details).

Elementary (primary) symptoms principle



Carl Wernicke (1848-1905)



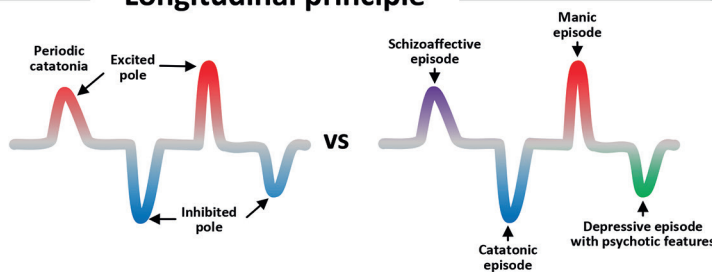
Mental illness affects only a limited part of brain functioning causing specific elementary symptoms in one neuropsychological domain (emotion, thought, or psychomotricity) which in turn induce secondary symptoms.

ICD-DSM: One part of the brain is affected independently for each symptom of a mental illness

Longitudinal principle



Karl Kleist (1879-1960)



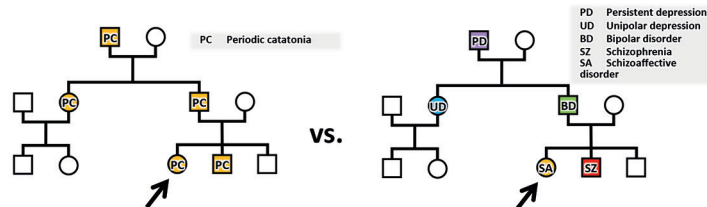
If an individual presents several clinical pictures over time, he or she is affected by the same pathology, presenting with different manifestations.

ICD-DSM: If an individual presents several clinical pictures over time, Sydenham's principle overrules the single liability thesis.

Family aggregation principle



Karl Leonhard (1904-1988)



If several members of the same family present with an endogenous psychosis, they are likely to share the same liability.

ICD-DSM: If several members of the same family present with different psychotic manifestations, Sydenham's principle overrules the single liability thesis.

Box 1.

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

Validity assessment of WKL phenotypes

The *construct validity* of a phenotype encompasses many different properties. Firstly, to comply with the logical positivist's call for objectivity, a phenotype must be reliable,¹³ and this *reliability* is assessed by inter-rater reproducibility. Secondly, the fulfillment of the naturalistic assumptions behind the concept of a phenotype could be supported by its predictive, face, differential, and taxonomic validities. Test-retest reproducibility will not only be considered here as a measure of *predictive validity*¹⁴ but also of *face validity*, ie, how closely patients match the "typical" definition and to what extent it accounts for all of the patients' manifestations.¹⁵ Indeed, it shows that phenotype descriptions are either comprehensive enough to include all possible clinical pictures or focus on an unchanging symptom-complex for the diagnosis to remain lifelong stable. Hence it avoids resorting to comorbidities other than behavioral complications, eg, drug abuse. *Differential validity* looks for the selective associations of a phenotype with *external validators* through head-to-head comparisons. These can be any clinical, contextual, or biological features that are not part of the original description,¹⁶ eg, age of onset, familiarity, gender difference, treatment response, any biological parameter etc. Finally, *taxonomic validity* appraises the fulfillment of the categorical structure of the phenotypes through taxometric analyses.¹⁷

Validity per se demands a *biological causal model* accounting for a phenotype. The model validity is assessed through a two-step process acknowledged as the "*theory of proof*"¹⁸ in medicine: the demonstration of a strong *correlation* with the biological cause and the outbreak or the alleviation of the phenotype with the *experimental* manipulation of the cause. It has mainly been investigated in periodic catatonia.

Overview of WKL classification

The field of endogenous psychoses

The WKL classification is limited to the field of endogenous psychoses. *Psychosis* does not have the same meaning here as in the *DSM* or the *ICD*. It is not restricted to hallucinations or delusions, but stands for a wide range of specific emotional, cognitive, and behavioral disturbances, supposed

to be mainly accounted for by some *qualitative disturbances* of one cerebral process, ie, naturalistic assumption. It is opposed to the old concept of "neuroses" which putatively results from nature-and-nurture-interactions, eg, the maladaptive response of a given personality coping with a specific life event. These are *complex diseases* mixing trait risk factors (addition of multiple causes of very small effect, ie, normativistic) interacting with other factors, ie, synergistic assumptions.⁴

The WKL phenotypes deserve to be contrasted as credible alternatives with other approaches currently under discussion

The *endogenous* feature refers to Kraepelin's, Jaspers', or Birnbaum's tripartite system in which psychiatric symptoms could be organic (exogenous, ie, secondary to a medical condition including substance-related), reactive (neurotic) or endogenous.¹⁹ Endogeneity assumes a single cause, which yet remains to be discovered.

While the *ICD* and the *DSM* distinguish exogenous disorders, the endogenous - neurotic distinction, which could be rephrased as simple vs complex diseases, has completely disappeared due to the endorsement of the atheoretic principle.¹³ Consequently, on the psychotic side, psychotic post-traumatic stress disorder, psychotic body dysmorphic disorder, or stress-related brief psychotic reactions, as observed in borderline personality disorder, are not endogenous psychoses. Yet the largest differences lie on the affective side. Reactive, eg, bereavement, and neurotic depressions, which probably account for most major depressive disorders,²⁰ are not part of the endogenous psychoses in the WKL perspective. It is worth reminding the endogenous-neurotic distinction has been repetitively supported by taxometric analyses of depressive disorders.²¹

While most WKL phenotypes are within the scope of affective and psychotic *ICD* or *DSM* disorders, there are some exceptions, eg, some system schizophrenias might be diagnosed in the autistic spectrum or in cluster A personality disorders.

Basic features and relationship with consensus classifications

The WKL school defines 35 phenotypes, accounting for about 90% of endogenous psychoses²² (*Table I*). To achieve this, descriptions do not focus on what phenotypes have in

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Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

COURSE	FAMILY	NEUROPSYCHOLOGICAL DOMAINS			POLARITY	
		AFFECT		THOUGHT		PSYCHOMOTRICITY
Relapsing-remitting	Phasic affective psychoses	Pure depressions (D)	Pure euphorias (E)		Mono-polar	
		Agitated D	Unproductive E			
		Hypochondriacal D	Hypochondriacal E			
		Self-torturing D	Exalted E			
		Suspicious D	Confabulatory E			
		Non-participatory D	Non-participatory E			
		Pure mania				
		Pure melancholia				
	Manic-depressive illness				Bipolar	
	Cycloid psychoses	Anxiety-happiness psychosis	Excited-inhibited confusion psychosis	Hyperkinetic-akinetic motility psychosis		
Progressive relapsing	Non-system schizophrenias	Affect-laden paraphrenia	Cataphasia	Periodic catatonia		
Progressive	System schizophrenias	(System) hebephrenias (H)		System paraphrenias (P)	System catatonias (C)	Mono-morphic
		Foolish H		Hypochondriacal P	Parakinetic C	
		Eccentric H		Voice-hearing P	Pseudo-compulsive C	
		Shallow H		Incoherent P	Proskinetik C	
		Autistic H		Fantastic P	Negativistic C	
		Combined H n=6		Confabulatory P	Short-circuit-speech C	
				Expansive P	Absentminded C	
				Combined P n=15	Combined C n=15	

Table I. Overview of the WKL phenotypes (inspired by ref 97). Only the 35 major forms are displayed; the 36 minor forms are two by two combinations of system schizophrenias. See *Appendix 2* for the consensus on the English translation.

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

common, but rather in what aspects they differ from one another. For instance, positive symptoms might occur in many phenotypes and hence are not helpful per se. Moreover, in contrast to *ICD/DSM*, symptoms have no meaning by themselves but only as part of a specific symptom-complex organized according to the primary-secondary principle (*Box 1, Appendix 2*).

Phenotypes are grouped into five families^{22,23} according to their course, mono- or bipolarity, and their primary affected neuropsychological domains: affect, thought, and psychomotricity (*Table I*). There are one monopolar, three bipolar, and one monomorphic families, gathering not 1 but 12 monopolar affective phenotypes and not 1 but 7 bipolar phenotypes. According to the WKL perspective, the term “*schizophrenia*” only applies to phenotypes with residual symptoms which encompasses one bipolar and the monomorphic families.

The WKL classification is strikingly different from consensus ones. While *ICD-10* and *DSM-IV* have a concordance of $\lambda=0.86$ with one another, WKL clearly gathers patients differently since its concordance is only of $\lambda=0.4$ with *ICD-10* and of 0.56 with *DSM-IV*.²⁴

Reliability of WKL phenotypes

On average, WKL phenotypes are highly reliable with 97% of inter-rater diagnostic consistency when performed by expert raters, giving an average kappa value of 0.82 to 0.93.^{25,26} In comparison, consensus disorders have kappa values of 0.84 for schizophrenia, 0.71 to 0.83 for bipolar disorder, and 0.22 for schizoaffective disorder.²⁷

Test-retest reproducibility, prognostic and face validity

In prospective studies, the test-retest reproducibility at 15 years, follow-up was 93% and ranged from 76% to 93% at 33 years follow-up.^{28,29} This stands well even in comparison to the much broader *ICD* diagnosis of schizophrenia which remains consistent in 90% of the patients in retrospective chart review after a follow-up of 25 years.³⁰

Differential validity of the main phenotypes

Monopolar affective phenotypes with purely relapsing-remitting course

Pure melancholia and pure mania

Pure melancholia and pure mania are monopolar affective

phenotypes.³¹ The term “*monopolar*” is used here rather than “*unipolar*” to emphasize the differences between the original WKL concept and consensus classifications. Monopolarity implies symptomatic stability both within and between the episodes, ie, *monomorphy*, as well as the absence of mixed or incomplete states (see manic-depressive illness). Hence, monopolarity applies also to the manic pole. The independence of the pure mania phenotype has been replicated in the Zurich cohort.³² While grounded in the affect, pure mania and pure melancholia characteristically also affect the other domains, eg, drive, speed of thought, and psychomotricity.

The prevalence of pure melancholia is many times higher, accounting for up to 10% of endogenous psychoses, whereas pure mania is below 1%. The course is purely relapsing-remitting with an average of 12 months for an episode of melancholia.³³ Symptoms typically respond to usual antidepressant or antimanic therapeutics. Both phenotypes have little inheritance with 3% of affected first-degree relatives which significantly differs from manic-depressive illness (22% to 36%).^{34,35}

Pure depressions and pure euphorias

These are also relapsing-remitting monopolar phenotypes, ie, monomorphic without mixed or incomplete states (see manic-depressive illness, MDI).³¹ The five pure depressions and the five rare pure euphorias are characterized by specific disturbances of distinct emotional systems within the affective domain sparing thought, drive, and psychomotricity. They often go along with characteristic delusions or hallucinations: delusional guilt in self-torturing depression, persecutory ideas in suspicious depression and unpleasant bodily sensations in hypochondriacal depression. These may be *ICD*-diagnosed as depression with psychotic features or schizoaffective disorders. These phenotypes only account for 4% of inpatients with endogenous psychoses.³³ In contrast to pure melancholia, their episodes typically last years with progressive beginnings and endings³⁶ and they are less responsive to therapeutics.^{36,37} They also have a low familiarity when compared with MDI (3% vs 22% to 36%).^{34,35}

Bipolar phenotypes with purely relapsing-remitting course

In the WKL sense, bipolarity is not limited to affective disorders but extends to schizophrenia-like psychoses as

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

well. Only manic-depressive illness belongs to the affective disorders in the narrower sense.

Manic-depressive illness

MDI³¹ is the most frequent bipolar phenotype, accounting for 19% of patients with endogenous psychoses.³⁵ Even though the *ICD/DSM's* concept of bipolar disorder stems from the WKL-MDI one, there are major differences. Episodes have distinctive clinical features allowing MDI to be diagnosed even in patients having depressive recurrences only, in most cases from the first episode.³⁸ Affective episodes are characterized by their polymorphic manifestations and the mixed or incomplete features, both being currently rediscovered under the emerging concept of bipolar depression.³⁹ Clinical manifestations are qualified as polymorphic because they change within and between episodes. The span of MDI's clinical presentations is so large that it can mimic any monopolar or cycloid picture, yet generally not in a stable way. The trigger for these phenotypical changes can be endogenous, but these patients are also highly reactive to external events. For instance, patients can be talkative and lively during the interview, showing no outer manifestation of depression, while apathy and suffering can come back as soon as they walk out of the office. Such mood reactivity can also be observed in neurotic forms, but then of lesser magnitude. Mixed states are defined as the co-occurrence of both the manic and depressive pole among the different domains: affect, thought, and psychomotricity. This can be seen for instance in the combination of inhibited affect (sadness), excited thinking process (racing thoughts), and excited psychomotricity (agitation).³⁸ Incomplete states are an extension of the former concept, meaning that aside from being excited and inhibited, a single domain can also be completely unaffected. For instance, affect and psychomotricity might be inhibited while the speed of thought might be normal.

On average, MDI episodes are of shorter duration than monopolar ones, ie, 6 months on average for depressive episodes.³³ Acute onset, sudden cessation; or rapid switches are common. This phenotype shows more frequent relapses than monopolar phenotypes and this tendency tend to increase with aging.³³

The hereditary burden of MDI is significantly higher than for monopolar affective phenotypes and cycloid psychoses, with 22% to 36% of affected first-degree relatives.^{34,35,40}

There are two reasons for the familiarity of MDI to exceed the one of *ICD/DSM* bipolar affective disorder (9%).⁴¹ Firstly, as the MDI diagnosis can be made early, even if the clinical presentation is purely depressive, most intra-familial incongruencies vanish as nearly all of the (pseudo-) unipolar patients are diagnosed as MDI.⁴² Secondly, *ICD/DSM* bipolar disorder subsumes some cycloid psychoses which have low familiarity.

Cycloid psychoses

Cycloid psychoses are bipolar phenotypes of purely relapsing-remitting course. They have more intense psychotic manifestations, and are hence routinely diagnosed by *ICD/DSM* as schizoaffective or schizophrenic disorders. There are three different cycloid psychoses corresponding to the predominantly affected domain within which they quantitatively oscillate between opposite extremes. These are referred to as “poles,” organized into three axes:

- Hyperkinetic-akinetic motility psychosis in the psychomotor domain
- Anxiety-happiness psychosis in the emotional domain
- Excited-inhibited confusion psychosis in the thought domain.

Cycloid psychoses represent 20% of all endogenous psychoses.³⁵ Their clinical manifestations are highly *polymorphic*, due to rapid changes in the intensity and even in the polarity of the manifestations within the same episode. Importantly however, the opposite poles always manifest successively and never at the same time.

The *ICD-10* diagnosis of “acute and transient psychotic disorders” or ATPD (F23), was designed to embody these phenotypes together with the “*bouffées délirantes aiguës des dégénérés*”⁴³ or BDA (acute delusional outburst of the degenerates).⁴⁴ Yet, studies have found that ATPD only overlaps with the BDA and cycloid diagnoses in half of the cases.^{44,45} Furthermore, cycloid psychoses are defined as lifelong phenotypes, while BDA and ATPD are only defined as episodes. Hence the latter diagnoses are instable on follow-up: a third of initial BDA switches to schizophrenia or schizoaffective disorder after 10 years,⁴⁶ while it happens in half of initial ATPD after 5 years.⁴⁷

Cycloid episodes usually last between 1 to 3 months, and have acute onset and ending in up to two thirds of the cases.³³

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

Yet, these two features are neither sensitive nor specific enough to be used as diagnostic criteria.⁴⁸ The relapsing-remitting course means that, in the interepisode interval, patients develop full insight about their illness and do not present significant residual symptoms whatever the number of recurrences.^{48,49} Cycloid psychoses might be related to minimal brain damage. Unspecific MRI abnormalities are more frequent relative to non-system schizophrenias, eg, enlarged ventricles, white matter hyperintensity, or small cortical defects.⁵⁰⁻⁵² These might be acquired early: mothers of cycloid patients report significantly more infections of the upper airway during the first trimester of pregnancy, childbirth complications are more frequent and seasonality of birth is larger in cycloid phenotypes relative to controls and non-system schizophrenias.⁵²⁻⁵⁴ Conversely, the heritability of these phenotypes is low, with only 5% of affected first-degree relatives, indistinguishable from controls and significantly lower than in MDI, cataphasia, and periodic catatonia.^{34,35,40,55}

Patients affected by cycloid psychoses are more vulnerable to precipitating factors: stress, sleep disorders, cannabis, etc. Women are especially sensitive to estrogen drop: 88% of episodes start in the luteal phase, which is significantly higher than for any other phenotype.⁵⁶ Accordingly, cycloid phenotypes account for 60% of postpartum psychoses, with motility psychosis accounting for 36% on its own.⁵⁷

Antipsychotics shorten the episodes but should be used with caution in motility psychosis, which is especially at risk for neuroleptic malignant syndrome.⁵⁸ They are also effective in relapse prevention, bearing in mind that these patients are especially sensitive to their side effects. The maintenance of too-high doses of first-generation antipsychotics after remission favors post-psychotic depression and abulia, so that otherwise fully remitted cycloid patients might appear to suffer from residual schizophrenia.⁵⁹ Yet, once maintained for more than a month, the rapid discontinuation of antipsychotics increases the risk of relapse to a point that was unknown in the pre-neuroleptic era,^{59,60} raising the hypothesis that most these relapses might be induced dopamine supersensitivity psychosis.^{59,60} Mood stabilizers not only help as an add-on treatment in the acute phase, but might also be considered as viable alternatives to antipsychotics in the maintenance phase considering their decent relapse prevention.⁴⁸

Phenotypes with build-up of residual symptoms: the schizophrenias

In the WKL perspective, the term “*schizophrenia*” carries a prognostic value as these phenotypes progress toward a persistent residual state of which abulia is a frequent, though not characteristic, feature. WKL schizophrenias have phenotype-specific residual symptoms.

“System” and “nonsystem” schizophrenias have nothing to do with the concept of “delusion systematization,” ie, the logical organization of delusional ideas. Here, “*system*” must be understood analogously to the involvement of a specific biological function as in organic medicine, ie, system diseases. Regarding brain diseases, these systems are functional networks, eg, the pyramidal system is the one that degenerates in amyotrophic lateral sclerosis. Multiple systems can be affected, as in multiple-system atrophy, which combines the degeneration of extrapyramidal, cerebellar, and vegetative systems. Due to their clear-cut and life-long *monomorphic* residual symptoms, *system schizophrenias* are qualified as such because they are supposed to be accounted for by the impairment of such specific functional networks, whereas *non-system schizophrenias* are *polymorphic*, *bipolar*, and putatively involve many “systems.”

Non-system schizophrenias

There are three non-system schizophrenias characterized by a predominantly affected domain within which they can express both poles. In contrast to cycloid psychoses, changes are not purely quantitative, but also *qualitative*, with symptoms from both poles occurring together. Because of their bipolarity, they show a broad, yet specific, clinical spectrum. They mostly run a progressive-relapsing course and develop a characteristic set of residual symptoms of increasing severity. All have a specific heredity burden, *without crossed liability*. Interestingly, domain-specific attenuated symptoms have been reported in nonpsychotic relatives, especially in obligate carriers.⁶¹ As a whole, nonsystem schizophrenias respond much better to antipsychotics^{62,63} and to the addition of mood stabilizers³⁷ compared with system schizophrenias. However, treatments mostly improve acute manifestations but have virtually no effect on residual symptoms.

Affect-laden paraphrenia is a schizophrenic bipolar phenotype of the affective domain. It only accounts for 5% of

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - Foucher et al

endogenous psychoses but for 10% of ICD/DSM psychotic disorders.^{33,35} Its various clinical presentations have been independently described by many authors under various names around the world.^{46,64-66,46,67-69} The WKL school subsumed them under the same phenotype because individuals could change from one clinical picture to the other and because relatives could display one of the other clinical pictures (Box 1).⁷⁰ The core of affect-laden paraphrenia is a *paranoid mood* which encompasses the strong mistrust, irritability and hostility of one pole blended with the feeling of self-importance of the other pole. This specific affective state leads to more or less systematized delusions of persecution and grandiosity often accompanied by multimodal hallucinations.⁷¹ The residual picture is the *irritated reference syndrome*, which is a delusional construction about intentions of specific others regarding oneself. Besides the pathological affect underpinning the delusions, emotional responses dampen over time. A feature that repeatedly impressed many authors was the contrast between the *judgment errors*, up to the acceptance of fantastic ideas, with a generally *well-organized thought process* which is constant out of the episode.^{46,64,69} The course is mostly progressive-relapsing. Over 10 to 30 years, patients develop increasingly pervasive reference ideas of more and more fantastic coloring. Yet they remain able to adapt to the interviewer in superficially denying their delusions.

Antipsychotics help in blunting the affective pressure that ensues, but also fuels the delusions, yet never allowing the patients to fully distance themselves from their ideas (84% of responders).^{62,63} The median age of onset is 36 years, but is highly variable explaining late-onset cases. The phenotype has an autosomal recessive inheritance pattern with 12% of affected siblings vs only 2% of affected parents.^{34,35} There is also a significantly larger number of patients born from consanguineous weddings relative to other schizophrenias and cycloid psychoses (3.3% vs 1%).^{56,61}

Cataphasia (schizophasia) is a bipolar phenotype mainly affecting thoughts and language. It accounts for about 8% of endogenous psychoses and its estimated prevalence is about 0.1 to 0.2% in Germany.⁷² Its excited pole was first described by Kraepelin under the label “*schizophasia*.” The observation of multiplex families allowed to relate this clinical picture to its counter-pole dominated by thought inhibition.⁷³ The core of the phenotype is a specific thought and language disorganization with incoherence and logical

derailment coming with syntactic and semantic errors, eg, paragrammatism, paraphasias, and neologisms. These core symptoms need to be specifically investigated, especially in the residual phase. As everyday concrete thinking is less affected, they frequently remain discreet in ordinary conversations and behavior. The *thought and language test*, a standardized WKL examination procedure that challenges abstract thinking, greatly sensitizes the detection of cataphasic features.^{72,74,75} Language errors must be appraised in the context of patients’ skills, so are hence harder to ascertain in non-native speakers; in such cases they may be secured by long-term follow-up re-examination. As the disease progresses, nonspecific fluctuating persecutory ideas might remain but are secondary to the core residuum which impairs patients’ understanding, leading to misinterpretations in close similarity with residual Wernicke’s aphasias.⁷⁶ During episodes, patients exhibit a variety of affective and psychotic symptoms, that are frequently in the foreground.

Although the episodes respond to antipsychotics (up to 78% using first-generation drugs),^{62,63} the specific symptoms are treatment-resistant. The association of thought disorganization with emotional turmoil make cataphasic patients particularly at risk for suicidal behavior (52% of patients) and deaths by suicide (18% of patients).⁷² The phenotype shows familial aggregation, with 15% to 25% of affected first-degree relatives, on top of which 12% of non-psychotic first-degree relatives also show milder forms of the typical thought and language disorganization.^{34,35,72} A genetic locus has recently been found for cataphasia on Chr11p, the strongest association being found with a gene coding for cathepsin-D, a lysosomal protease which mutations can cause neurodegenerative storage disorder (Roth et al, unpublished material).

In accordance with their residual thought and language impairments, cataphasic patients have a specific dysfunction of their temporoparietal junctions bilaterally; these are hypoactive and functionally disconnected.⁷⁷ This fits with multimodal imaging results showing that the same cortices, together with their underlying white matter, were hypo-myelinated and had an increased iron content (Foucher et al, unpublished material). Considering that the latter could likely result from microglial activation, these findings are in line with those reported in cathepsin-D deficits,⁷⁸ suggesting a neurodegenerative model for cataphasia.

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

Periodic catatonia is roughly as common as cataplexy, accounting for about 7% of patients suffering from endogenous psychoses. Despite its name, WKL's periodic catatonia should not be viewed as the mere recurrence of *IDC/DSM* catatonic episodes.⁷⁹ Beyond mere global bipolar quantitative motility changes, the core of this phenotype is a specific disorganization of psychomotor functions, ie, mostly affecting expressive and reactive movements. The qualitative changes manifests as the *mixing* of both akinesia and hyperkinesia but to different body parts, eg, rigid hypokinesia of the upper limb together with facial restlessness. Other qualitative anomalies are *parakinesias* that alter simple movements, making them appear stiff and/or jerky, or distort expressive movements, especially the mimics, going as far as grimacing.⁷¹ These are currently rediscovered under the name of spontaneous dyskinesias.⁸⁰ However, parakinesias have a wider spectrum and distinctive features that allow them to be differentiated from tardive dyskinesias.⁸¹ The residual state includes the persistence of these characteristic psychomotor anomalies together with abulia, while residual psychotic symptoms are rare. The social or occupational impairment is highly variable (GAF = 57±19 after an average of 13 years of progression).^{77,82}

This phenotype is responsive to antipsychotics (60% of responders with first-generation drugs),^{62,63} but also sensitive to their extrapyramidal side effects, hence its large response increment after switching to clozapine.^{37,83} It further benefits from benzodiazepines⁸⁴ and electroconvulsive therapy which are inefficient in system catatonias.⁸⁵ Yet all therapeutic efforts can only help coping with exacerbations but fail to improve the specific residual symptoms.

At the *etiological level*, several studies have confirmed the high heritability of periodic catatonia, with 21% to 26% of affected first-degree relatives,^{34,35,83} which is significantly larger than for system catatonias (4%).²⁵ Considering the extended phenotype, ie, including nonpsychotic relatives with only psychomotor signs, the percentage raises to 32% to 41% of affected first-degree relatives.^{86,87} Transmission is autosomal dominant with incomplete penetrance and anticipation. Two genome-wide linkage studies found a major susceptibility locus on Chr15q accounting for about two thirds of the pedigrees (OMIM 605419).^{88,89} This has recently been supported by an association peaking in an intergenic region between *CGNL1* and *GCOM1* (Gawlik et al, unpublished material), the latter being implicated in an NMDA-dependent

neuroprotection pathway that might be especially important for GABAergic interneurons.⁹⁰ Yet periodic catatonia is likely to be genetically heterogeneous: other pedigrees matched on other loci, eg, Chr21q13-ter.⁸⁹ The unity of the phenotype might be better explained at the *pathophysiological level*. Based on previous literature, especially on the independent replication of its specific left premotor hyperactivity^{91,77} when compared with other psychoses, periodic catatonia is currently modeled as an acquired deficit of intra-cortical inhibition possibly ensuing the degeneration of GABA interneurons. As a first validation step, the strength of the correlation between left premotor hyperactivity and the phenotype was prospectively tested in individual patients by comparing a new group of periodic catatonias to other psychoses, including system catatonias. The association was found to be both sensitive (98%) and specific (88%), making the case for this functional imaging measure to be a viable biomarker.⁹² As interventional validation step, personalized rTMS was used to correct left premotor inhibition deficit. Not only did the improvement of residual symptoms resulted in substantial functional gains, but was also specific for premotor targets (vs prefrontal and parietal ones) and for periodic catatonia (vs system catatonias).⁹³

System schizophrenias

System schizophrenias account for 21% of inpatients with endogenous psychoses.³³ They have an insidiously progressive course resembling that of slow encephalitis. They begin with a *process phase* of 1 to 5 years, in which unspecific dysthymic and psychotic manifestations can accompany the growth of a distinct symptom-complex, presumably due to the deterioration of a specific system. After processual symptoms vanish, the residual clinical picture will remain unchanged up to the end of the patient's life, ie, monomorphic.⁹⁴ Phenotypes are ordered according to the domain to which belongs the affected system:

- The four phenotypes of hebephrenias share a specific disturbance of judgement emotions which leads to affective flattening and loss of initiative. Judgement emotions are the one needed to evaluate non-concrete and non-present issues such as the course of life
- There are six major phenotypes of system paraphrenias having specific combinations of hallucinatory and delusional features
- System catatonias consist of six varieties of definite qualitative psychomotor impairment.

Original article

Validity of Wernicke-Kleist-Leonhard phenotypes - Foucher et al

The three subfamilies have different age of onset: 24 for system catatonias and 23 for hebephrenias, but 36 for system paraphrenias.³³ No significant hereditary burden has been reported. The percentage of 2% to 4% of affected first-degree relatives is not significantly different from what is seen in controls but significantly different from periodic catatonia.^{25,34,35,83} In system catatonias, 34% of the mothers report an infection of the upper airways during the second trimester of pregnancy which significantly differs from periodic catatonia (8%).⁹⁵ Neuroimaging reveals significantly more cortical atrophy in system schizophrenias than in non-system phenotypes.^{96,97} Finally, contrary to other phenotypes, interventions have little or no effectiveness: antipsychotics (1% to 40% of responders to first-generation antipsychotics),^{62,63} no advantage for clozapine,^{37,83} ECT, mood stabilizers, or antidepressants.³⁷

Conclusion

In accordance with the biomedical paradigm, the WKL School has empirically optimized the descriptions of putatively natural phenotypes inspired by neuroscience and based on common medical heuristics. They are reliable, they have good predictive validity and differential validity regarding

gender ratio, age of onset, familiarity (without crossed-heritability), pregnancy complications, and response to treatment. Only their taxonomic validity deserves to be further evaluated. While the biological model for cataphasia remain to be tested, the one for periodic catatonia has already been supported by correlational and interventional evidence.

Despite their elaboration in the purest tradition of the biomedical paradigm, yet diverging from dominant paradigms, these phenotypes received poor attention from basic researchers (see also *Appendix 2*). On the other hand, clinicians value them for their long-term stability and their prognostic and therapeutic relevance. We hope that this review will contribute to revive the interest of the psychosis research community for this research program which deserves to be confronted with others in an adversarial collaborative way.⁴ ■

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WKL international society consensus on English nomenclature

Introduction: a question of nomenclature

For readers familiar with Leonhard's own words, some of the terms used in the current document might be confusing. Some are different from the terms that were used in the previous translations of Leonhard's books.

The Wernicke-Kleist-Leonhard international society (WKLIS, <http://www.wkl-society.de>) has endorsed two primary goals: first, the diffusion of the knowledge from this school of thought and the promotion of research based on a differentiated psychopathology; second, the preservation of the "tradition" or a sort of "orthodoxy" of its original contribution, ie, the classification of endogenous psychoses. The latter should not be viewed as the preservation of an old-fashioned practice but of a clinical expertise that has dramatically vanished after 40 years of *DSM* domination.

The current rejection of the "*DSM-III* research program" renewed the need to improve knowledge of the research community on what looks to be a promising alternative to break the deadlock. We felt, however, that a too-literal translation of the original German terms, cited in the 1960s for the latest, might be misleading, as they have different significance nowadays. Moreover, it might bias the vision of the community towards a pure historical account, whereas its medical and neuroscientific vision is of tremendous modernity.

This nomenclature's refreshing induces a dilemma regarding our two major goals as it apparently opposes the preservation of the "traditions." However, this is only an appearance, as the idea is to capture these original concepts at best using current terminology.

Here are short accounts for the motivation behind these changes. They were submitted to the coauthors of the main article using a web survey. Everybody agreed upon the

need for a modernization and a standardization of the WKL English (n = 16/16; 100%). By supporting the publication of this article, the WKL International Society formally endorsed these changes.

Naming the courses

We proposed copying the neurological naming of the course for chronic diseases such as multiple sclerosis.

1. Relapsing-remitting labels psychoses' course of periodic symptomatic exacerbations, ie, relapses that completely remit thereafter, whatever the number of relapses, hence having "free intervals" with no (new) manifestations (*Figure 1a*). The term "remission" means that the patient has returned to his or her original state but remains susceptible to relapse and thus cannot be said to be healed. Leonhard's terms of "*phasischen Psychosen*" (phasic psychoses) come with this idea but does not apply to cycloid psychoses despite their similar course.

2. Progressive-relapsing labels psychoses' course of periodic symptomatic exacerbations, ie, relapses, that are not followed by complete remissions, ie, with accumulating residual symptoms (*Figure 1b*).

3. Primary progressive labels psychoses' course of progressively accumulating residual symptoms during a so-called "process phase." Accessory symptoms can be observed during this initial period, which disappear after it. The residual manifestations will remain unchanged (monomorphic) up to the end of the patient's life (*Figure 1c*).

Apparently secondary progressive forms are supposed to be subsumed to either a progressive-relapsing or primary progressive course. In the latter case, accessory symptoms of the process phase are taken for an acute exacerbation.

Appendix 1

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

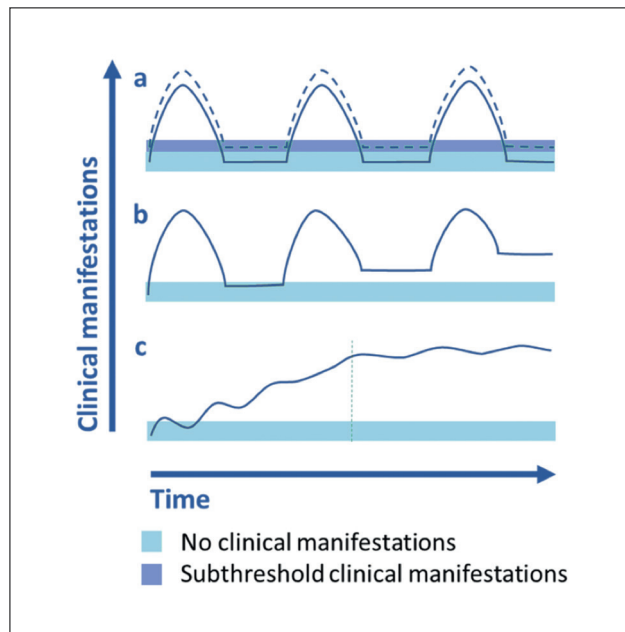


Figure 1. Main courses in the WKL framework. a. Relapsing-remitting; b. progressive-remitting; c. Primary progressive.

System vs nonsystem schizophrenias

The German words are “*systematischen*” and “*unsystematischen Schizophrenien*” which were translated as “systematic and unsystematic schizophrenias” in the two previous translations.

The first was in 1979⁹⁸ by the “Washington School of Psychiatry. Eli Robins (1921-1994), Georges Winokur (1925-1996) and Samuel Guze (1923-2000) were from the psychiatric department at Washington University in St. Louis. They were influential contributors to the operationalized criteria movement, eg, those of the so-called Feigher’s criteria. George Winokur is credited for having introduced Kleist, Leonhard, and Neele’s concept of bipolar and mono-/unipolar distinction in the United States. Last, the Washington school pleaded for a naturalistic research program and opposed the nominalist approach endorsed by the *DSM-III* task force headed by Robert Spitzer (1932-2015).

The second was done in 1999⁹⁹ by the “Würzburg school of psychiatry.”

It is of interest to recall that before endorsing Kleist’s “neurological system” vision, Leonhard called them, like Mitsuda, “typical” and “atypical” schizophrenias (“*typische und atypische Schizophrenien*”).

As stated in the main text, Kleist’s vision under “*systemkrankungen des Gehirns*” (system diseases of the brain) was the same as in neurology, ie, the impairment of specific neurological circuits or systems. While he distinguished between “neurological” and “psychic” systems, the latter being implicated in higher-order neuropsychological domains, the idea remained the same. Instances of neurological systems are the pyramidal, the extrapyramidal, the cerebellar, or the vegetative systems. Amyotrophic lateral sclerosis is an example of a degeneration of the pyramidal system. Importantly, it differs from a “localization syndrome” as it involves the system at several levels, ie, Betz’s pyramidal neurons of the motor cortex (upper motor neurons) and spinal motor neurons (lower motor neurons). Other degenerative diseases involve multiple systems, such as multiple-system atrophy (degeneration of the extrapyramidal, cerebellar, and vegetative systems.)

To come back to our nomenclature question, the “systematic” and “unsystematic” translations come with two issues. Firstly, they convey some confusion with the concept of “systematization” of delusional ideas. Second, it is not the way they should be translated according to the neurological nomenclature. The latter uses “system” diseases for Kleist’s “*systematisch*” concept. Hence, we proposed to use “system” and “nonsystem” to solve both problems (n = 14/15; 93%)

Neuropsychological domains vs psychic systems

The original words of “*psychischen Systeme*” can only be found on p 120 of the 8th edition of the textbook.¹⁰⁰ It has been translated as “psyche system” in the 1979 translation and “psychic systems” in the 1999 one. Importantly, however, it does not refer to the large domains that are thoughts, emotions, and psychomotricity—Kraepelin talked about “*Denk-, Wahrnehmungs- und Sprachstörung*,” “ie, disorders of cognition, affect and volition—but to one system in a domain. The Würzburg school uses the term “*Hauptebenen*” which can be translated as “main levels.” However, following Werner Strik and his colleagues,¹⁰¹ we propose to use “domain” to name these large fields

Appendix 1

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

ORIGINAL GERMAN NAMES	POSSIBLE XTRANSLATIONS	NOTE	REMARK	SURVEY	%
Manisch-depressive Erkrankung (n = 9)	Manic-depressive psychosis	1999 translation		4	44%
	Manic-depressive disease	1979 translation		0	0%
	Manic-depressive illness	Alternative proposal		5	56%
Gehetzte Depression (n = 8)	Agitated depression	1999 translation	Close to current understanding	8	100%
	Harried depression	1979 translation	Possible confusion with self-tortured	0	0%
Selbstquälerische Depression (n = 8)	Self-tortured depression	1999 translation		0	0%
	Self-torturing depression	1979 translation		8	89%
	Harried depression	Alternative proposal	Possible confusion with agitated depression due to the former use of the term for it	0	0%
Schwärmerische Euphorien (n = 9)	Exalted euphoria	1999 translation		8	89%
	Enthusiastic euphoria	1979 translation		1	11%
Angst-Glück-Psychose (n = 9)	Anxiety-happiness psychosis	1999&1979 translation		7	78%
	Anxiety-blissfulness psychosis	Yadav (2010)		2	22%
Affektvolle Paraphrenie (n = 9)	Affective paraphrenia	1999 translation		0	0%
	Affect-laden paraphrenia	1979 translation		9	100%
Läppische Hebephrenien (n = 8)	Foolish hebephrenia	1999 translation		6	75%
	Silly hebephrenia	1979 translation		2	25%
Flache Hebephrenien (n = 9)	Shallow hebephrenia	1999 translation		9	100%
	Inspid hebephrenia	1979 translation		0	0%
Phonemische Paraphrenien (n = 9)	Phonemic paraphrenia	1999&1979 translation	Ununderstandable by non WKL psychiatrist	3	33%
	Voice-hearing paraphrenia	Alternative proposal	Understandable by non WKL-trained psychiatrist	6	67%
Manierierte Katatonien (n = 9)	Manneristic catatonia	1999 translation	Double meaning	2	22%
	Affected catatonia	1979 translation	Double meaning	0	0%
	Ritualized catatonia	Alternative proposal	Understandable by non WKL-trained psychiatrist	2	22%
	Pseudo-compulsive catatonia	Alternative proposal		5	56%

Appendix 1

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

Sprechbereite Katatonien (n = 7)	Speech-prompt catatonia	1999 translation	Possible confusion with real talkative behavior	2	29%
	Voluble catatonia	1979 translation		1	14%
	Short-circuit-speech catatonia	Alternative proposal	Avoid confusion with talkative behavior	4	57%
Sprachträge Katatonien (n = 7)	Sluggish catatonia	1999 translation	Direct translation of the German term	0	0%
	Sluggish-speech catatonia	1979 translation		2	29%
	Taciturn catatonia	Alternative proposal		0	0%
	Aloof catatonia	Alternative proposal		0	0%
	Dull catatonia	Alternative proposal		0	0%
	Hardly speaking catatonia	Alternative proposal		0	0%
	Absentminded catatonia	Alternative proposal	Focus on another important aspect of the phenotype	3	43%
	Inattentive catatonia	Alternative proposal		2	29%

Table 2. List of phenotypes with uncertain translations. The ones adopted are in bold.

of human's cognition. Each domain is made of several "systems," a term under which we will subsume both the (psychic) systems of the system schizophrenias, but also the "*Gefühlsschicht*" of (affective) monopolar phenotypes ("emotional plane" in 1999's translation or "emotional layer").

Moreover, "psychic" sounds outdated nowadays as if these processes would come with some additional "spiritual" aspect. Yet, Kleist and Leonhard only used the qualifier to stress the difference between "low-level" (neurological) and "high-level" (psychological) systems. Both are supposed to be implemented in the brain without any added "spiritual matter." Hence, the adjectives of "neuropsychological" or "neurobehavioral" were proposed instead of "psychic."

"Neurobehavioral" was again inspired by Werner Strik and colleagues¹⁰¹ who put forward that only behavioral outputs are observable and operative. Indeed, it is the term that has been adopted by the neurological specialty that is the closest to psychiatry, ie, behavioral neurology.

However, it was argued that "neuropsychological" better captured Wernicke, Kleist, and Leonhard's vision of the "psyche" while emphasizing the hypothesis of a neurological substrate for domains and systems (n = 10/13; 77%).

The "thought and language test" vs "psychic experimental test"

Initiated by Karl Kleist, the "*Psychisch-experimentelle Prüfung*" (psychic experimental test) is a way to test thinking, logic, and language (p101).¹⁰⁰ The way we currently evaluate conceptual disorganization in the Positive and Negative Syndrome Scale is a poor by-product of it. Beyond proverb interpretation and the similarities test (conceptualization), there are many important differences that make it unique as it allows some important differential diagnoses (cataphasia, system paraphrenias...).

The translation of "psychic experimental test" is poorly informative and again sounds outdated. "Test for Thought (Logic) and Language" (TTL) was proposed as a name, to indicate what it is used for (n = 13/16; 81%).

Appendix 1

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

Naming of specific phenotypes

The survey also proposed to define or even modify the English translation of some phenotypes. There were essentially two reasons for this. First, some phenotypes had been translated under different names in the English literature, eg, “*Affektvolle Paraphrenie*” was called affective or affect-laden paraphrenia. Future publications should be consistent in the naming in order to avoid confusion and to facilitate

literature search. Second, considering the semantic drift since the names were quoted, some translations might have been misleading, eg, “*Manierierte Katatonie*” which translation as “manneristic catatonia” does no more convey the idea of a highly ritualized behavior. Last, emphasis was put on the avoidance of stigmatizing labels. See *Table I* for the different proposals and the final choice endorsed by the WKL international society. ■

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Heuristics, creation of, and diffusion of WKL phenotypes

In this additional material, we provide a longer version of the heuristics that guided the empirical elaboration of WKL phenotypes outlined in *Box 1* of the main article, briefly describe how their use progressively allowed them to be sorted into categories, and discuss some of the reasons that could explain their poor spread in Western psychiatry.

Heuristics for phenotype optimization

Although the final elaboration of the classification was Karl Leonhard's, it wouldn't have been possible without the previous contributions of Carl Wernicke and Karl Kleist. Emil Kraepelin was also influential to him, not just by the dichotomy he introduced in the 6th edition of his "*Lehrbuch*," but by his later and forgotten attempt to refine the clinical descriptions as detailed in the 8th edition.¹⁰² Following Wilhelm Griesinger,¹⁰³ all of them embraced the *naturalist* view of the *biomedical paradigm*, and shared the strong a priori belief that endogenous psychoses are "brain diseases," against Karl Jaspers' influential criticism that they were "brain mythologists."¹⁰⁴ According to the naturalistic assumption, a disease comes from a single cause of major effect. If this effect is reasonably consistent, patients should have some homogeneity of appearance, allowing them to be described using a typical set of clinical manifestations, ie, *phenotypes*. This is the *principle of genera*,¹⁰⁵ also referred to as the *principle of Sydenham*.¹⁰⁶ The concept of "face validity" reflects the quality of this grouping according to patients' clinical presentations.

If responsible for a highly disabling condition, a cause should be under high *selection pressure* and hence *rare*. Accordingly, the cause and its consequences, ie, the phenotype, should be liable to the *principle of parsimony*.¹⁰⁷ This allows the addition of further heuristic characteristics that go far beyond the mere face similarity of clinical pictures, to find the most appropriate "typical" definition. All of them are simple specifications of the principle of parsimony.

Carl Wernicke (1848-1905): symptom complex and elementary symptoms

Like many psychiatrists of that time, Wernicke adopted the subdivision of mental activity into three main "neuropsychological" domains: affect, thought, and psychomotricity.¹⁰⁸ He was a pioneer in neuropsychology thanks to his clinical skills, acquired primarily in patients with brain damage from the Franco-German war of 1870.

Wernicke postulated that some symptoms were closer to the core cerebral correlate which he called *elementary symptoms* from which others could arise.^{109,110} This idea was later rephrased by Eugen Bleuler, as primary and secondary symptoms.¹¹¹ Wernicke further assumed that mental illnesses might result from the dysfunction of a limited part of the brain and tried to assign primary symptoms to the most elementary neuropsychological system (each domain is made of several systems) from which secondary symptoms could ensue. Thus, symptoms do not have diagnostic significance per se, but only as part of a "*symptom complex*."¹¹² The counterpart of this integrative approach is the highly differentiated symptomatology that occurs.

For instance, the clinical presentation of a motionless and mute patient, which would be diagnosed as "catatonic" according to the consensus diagnosis, could be split into at least three different phenotypes depending on the associated symptoms. In the case of a primary impairment of psychomotricity, specific "elementary symptoms" of psychomotor inhibition should occur: reactive and expressive movements should be more impaired than voluntary ones,¹⁰⁸ eg, "empty" facial expressions, while prompted movements should be relatively spared. Alternatively, immobility and mutism could be secondary to a primary thought inhibition in which case the impairment should dominate on spontaneous voluntary movements due to thought emptiness. Automatic movements might be unaffected or even increased due to a release

Appendix 2

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

phenomenon, eg, stereotypies. Moreover, a perplexed facial expression will often reflect the patient's worrisome lack of understanding of his or her environment. Finally, immobility and mutism can be secondary to a primary overwhelming affect, whether depressive, anxious, or ecstatic, paralyzing all mental and psychomotor activity. However, in this case postures and facial expressions should express the emotion that is later recalled by the patient.

Hence, isolated symptoms have no intrinsic diagnostic value. They must be interpreted in the context of the whole clinical presentation guided by a basic understanding of brain physiology. This implicitly undermines symptom checklist approaches.

Karl Kleist (1879-1960): the longitudinal principle and the catamnestic approach

The Alsatian Karl Kleist took over Wernicke's legacy and further developed this clinical expertise, guided by the expansion of the neuropsychological knowledge he acquired from the brain-damaged patients of World War I. His leading contribution was the decomposition of the principle of "unity of course and outcome,"¹¹³⁻¹¹⁵ enacted as a rule since its successful application by Antoine Bayle in the discovery of "general paresis,"¹¹⁶ the paradigmatic example of the discipline at that time. But Kleist dissociated the *prognosis* (or outcome) from the *longitudinal principle*. Patients might well not evolve up to the same point (prognostic principle), but even if the same patient has different clinical manifestations over time, these might not result from a large number of causes, but from one cause, which can be considered to be rare¹¹⁷ (longitudinal principle). The systematic application of this longitudinal principle came with a methodological correlate: optimizing phenotypic descriptions during life-long catamnestic follow-up¹¹⁸ rather than from mere (cross-sectional) clinical pictures. He pushed the idea to the point of building a special ward dedicated to these long-term observations in Frankfurt's university hospital; his idea was also applied by Leonhard, who did the same in Berlin's Charité university hospital. Kleist describes three major courses:

- Relapsing-remitting course, in which the patient gets back to his or her pre-episode state without residual symptoms, whatever the number of episodes, eg, manic-depressive illness, monopolar mood disorders, and cycloid psychoses

- Progressive-relapsing course, in which the repetitions of acute episodes are followed by incomplete remissions and occurrence of increasing residual symptoms, eg, nonsystem schizophrenias

- Primary progressive course in which the monomorphic residual state gradually takes place over a 1- to 5-year "process phase," eg, system schizophrenias. A course likely to be inspired by that of slowly progressive encephalitis.

Karl Leonhard (1904-1988): the family aggregation principle

Leonhard enhanced his predecessor's classification by adding the *family aggregation principle*. It is the third derivative of the principle of parsimony applied to multiplex families: if several members of the same family have an endogenous psychosis, they are likely to share the same (genetic) liability.¹¹⁹ This came with a methodological correlate: the systematic exploration of the affected family members in order to describe phenotypes that were coherent within the family, as illustrated by the case vignettes of his classification textbook.¹²⁰ As far as we know, this is unique in the field of psychiatry.

A step-by-step empirical elaboration

The different phenotypes did not emerge at once out of the blue. The *empirical* nature of the phenotypic description is illustrated by the step-by-step gathering of clinical presentations, catamnesis, and family exploration.

Monomorphic primary progressive forms (1936)

System schizophrenias were the first to be described. Their primary progressive course, ending within a few years in an unchanging monomorphic clinical picture, simplified their description. As this was the core of "*dementia praecox*," Emil Kraepelin had already proposed a first classification of their different clinical presentations in the 8th edition of his "*Lehrbuch*."¹⁰¹ Kleist expanded it and introduced the hypothesis of simple and combined neuropsychological system injuries. Last, in his thesis produced under Kleist's supervision,¹²¹ Leonhard resumed the phenotype description and further refined them, helped by his frequent visits to long-stay psychiatric hospitals where most of these chronically disabled patients were living.¹²²

Appendix 2

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

Monopolar relapsing-remitting forms (1949)

Kraepelin's manic-depressive illness was a catch-all for remitting psychoses. Their clinical presentations were described as any combination of excitation or inhibition of the different neuropsychological domains.^{101,123} The longitudinal principle made it possible to distinguish monopolar vs bipolar phenotypes. Kleist's concepts were first synthesized by Edda Neele (1910-2005) in her thesis.¹²⁴ The full descriptions of monopolar phenotypes were achieved first since they were simpler to describe (stable during an episode and identical from one episode to the other).¹¹⁹

Bipolar relapsing-remitting forms (1957)

It took a little bit longer to come to a more definitive description of the bipolar relapsing-remitting forms, ie, manic-depressive illness and cycloid psychoses.¹¹⁹ The latter were a major restructuring of the classification with motility and confusion psychoses, formerly part of Kleist's "marginal psychoses," brought together with anxiety-happiness psychosis. This new family, renamed "cycloid psychoses," gathers relapsing-remitting phenotypes with bipolar manifestations centered around one domain. Their phenotypical span is more limited than that of manic-depressive illness, but generally richer in psychotic symptoms.

Nonsystem schizophrenias (1961)

The major final step was the description of the schizoaffective bipolar progressive-relapsing forms which proceed toward specific residual states.¹¹⁹ These were difficult to separate from cycloid psychoses because they shared many features, while the progression might not be clearly perceptible during the early stage of the illness. Moreover, nonsystem schizophrenias can mostly or even exclusively only show one symptomatic pole in a patient, even with life-long follow-up, making the exclusive use of the longitudinal principle ineffective or even misleading. It was the family aggregation principle that provided the solution for their distinction. According to this heuristic Leonhard was able to distinguish periodic catatonia from motility psychosis and the other system catatonias as early as 1943. He was able to secure the grouping of the four forms of affect-laden paraphrenia described by Kleist into one common phenotype based on their observation in different members of multiplex families in the 1950s.¹²⁵ The same principle allowed him to identify and describe the inhibited

counterpart of Kraepelin's schizophasia,¹²⁶ leading to the creation of the coherent phenotype of cataphasia in 1961.¹²⁷ He continued to refine the description until 1968, when he published the final version of the classification, which served as basis for all the subsequent research within his framework of reference.¹²⁸

Reasons for the poor diffusion of the WKL phenotypes

Many of the WKL concepts have been studied and were influential in the shaping of some of *ICD/DSM's* entities, eg, bipolar and unipolar affective disorders, acute and transient psychotic disorders (respectively deriving from bipolar-monopolar and cycloid psychosis concepts). Yet, in deviating from the original descriptions, these entities lost their naturalistic value. The Saint Louis school brought up the bipolar-monopolar concept in the US because their distinct and specific hereditary burden was seen as an interesting "external validator." Unfortunately, the large difference observed in the WKL framework vanished in the *ICD/DSM* one. Regarding WKL's diagnoses, in manic-depressive illness, 22% to 36% of first-degree relatives are affected vs 4% for the monopolar phenotypes¹²⁸⁻¹³⁰; while in the *ICD/DSM* perspective, there are 12% of affected first-degree relatives in bipolar disorders and 15% in unipolar ones.¹³¹ The latter make more sense when converted into relative risk (10 vs 2) which takes into account the large prevalence of depressive disorders in the normal population. It is easily understandable that the WKL difference cannot survive the grouping of all depressive monopolar phenotypes, with MDIs having only depressive episodes on the one hand and all manic-euphoric phenotypes with some cycloid psychoses and the rest of the MDIs on the other hand; not to mention the gathering of (probably rarer) endogenous affective psychoses with (probably much more frequent) neurotic affective disorders. This could explain *ICD/DSM* apparent continuums such as the schizoaffective spectrum or the intermingling of affective with cluster B personality disorders. To preserve their qualities, the WKL phenotypes must be taken as they are, without adaptation (except if evidence-based). But who would agree to do so after being educated for years in a completely different tradition? Even curious minds might have been discouraged by the paradigmatic gap and the historical context; not to mention the mandatory use of the *DSM* to get a chance to be published in high-impact US journals. Lastly, learning

Appendix 2

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

the WKL framework as a “second language” is still far from being easy.

Most of the advantages of the WKL phenotypes derive from the *hierarchy of values* endorsed by this research program: naturality well above reliability (and simplicity). But when the classification reached maturity, in 1968, this was clearly conflicting with dominant conceptual frameworks: reliability was praised well above naturality, which could even be questioned considering the atheoretical stance. (This is unclear since the categorical nature of the *DSM* implicitly suggests the endorsement of some natural stances. In any case, the *DSM* values the pragmatic principle well above any other from basic science). Whereas the *DSM-III* research program sought an opinion-based consensus on the definition of disorders, the WKL research program sought only a consensus on the heuristics that could guide the observation-based optimization of phenotype descriptions. In a nutshell, the WKL framework embraced values and methods at odds with the prevailing *DSM* paradigm.

The gap was further enlarged by the *ideological and the historical context*. The leader of this research program was in the Eastern bloc. Leonhard headed the neuropsychiatric hospital of the Charité, in East Berlin, and was only allowed to travel out of East Germany in late life. The diffusion of his ideas was further impeded by the ideological war between liberal and Marxist humanisms which incited each world to disregard ideas coming from the other. West German psychiatrists could not escape from being influenced by the passionate eastern-bashing state of mind that prevailed in these times. With the marked exception of Helmut Beckmann and his followers (Würzburg school), no West German psychiatrist helped in the diffusion of WKL ideas, whereas many figures from other countries did, eg, Jules Angst (Switzerland), Carlo Perris (Sweden), Christian Astrup (Norway), George Winokur (USA), or Frank Fish (UK). Conversely, the WKL classification was very well known to most eastern European psychiatrists.

The major, persistent obstacle to the diffusion of WKL phenotypes is their *teaching*. Encouragingly, on the *theoretical side*, Leonhard’s reference book has been translated

into many languages. Yet it was written for German psychiatrists in the 1960s-1970s. Leonhard took for granted that his readers mastered the long tradition of German psychopathology which might no longer be the case nowadays. But most problematic is the teaching of *practical skills*. Leonhard wrote about signs and symptoms that are unfamiliar if not completely unknown to the *ICD/DSM* world, hence remaining unnoticed or unexplored. He further supposed the readers to be familiar with Wernicke’s diagnostic procedure (A procedure based on Wernicke’s “elementary symptom” – “symptom-complex” principle). Yet, this had only been described in Wernicke’s “*Grundriss der Psychiatrie*”¹³² (An outline of psychiatry), a book that was poorly known even in Germany, and had never been translated until 2015.¹³³ While rooted in the purest neurological tradition, this way to construct a diagnosis significantly differs from current practice: testing hypotheses about the primarily affected system vs checklist and operationalized criteria. Moreover, the WKL framework will generally be taught as a “second language.” Yet moving from *ICD/DSM* to WKL is not a simple matter of semantics; it does not consist of the mere use of different words for the same concepts, but of the learning of a new conceptual scheme. Most translations of WKL into *ICD/DSM* concepts (and vice versa) are coarse if not misleading, though difficult to refrain. Trainees will experience how deep our brains are biased by our *ICD/DSM* training: “we only see what our minds are prepared to comprehend” (Robertson Davies). Last, the mastery of this tool takes time while it (currently) gives no advantage in an academic career. This constitutes a strong negative bias in the selection of the people who are the driving force in the diffusion of ideas through teaching and publishing; not to mention the difficulty having article to be accepted when outside of the mainstream.

In short, while there were some paradigmatic and ideological-historical reasons for the poor diffusion of WKL phenotypes in the past, the biggest obstacle today is its teaching. The reading of the books and the articles only provides basic knowledge. Direct or video demonstrations by an expert remain essential to learn practical skills, while the mastery of the diagnostic procedure requires time-consuming training. ■

Appendix 2

Validity of Wernicke-Kleist-Leonhard phenotypes - *Foucher et al*

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