Appendix 2

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

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 rare[117] (longitudinal principle). The systematic application of this longitudinal principle came with a methodological correlate: optimizing phenotypical descriptions during life-long catamnestic follow-up[118] 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

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 synthetized 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 phenotypes[128-130]; 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

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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