Edward Shorter's comment on Jack R. Foucher et al.'s paper on Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: A review of their validity

Jack R. Foucher et al.'s reply to Hector Warnes' question

Differentiated psychopathology: a splitter methodological metatheory

We would first like to thank Hector Warnes for his queston: What [do the authors] mean by a "differentiated psychopathology"?

This expression summarizes the Wernicke-Kleist-Leonhard (WKL) approach in psychopathology. As far as we are aware, this expression stems from the Würzburg group at the time it was leaded by Helmut Beckmann. We cite the following from Prof. Gerald Stober (2007): "*Helmut Beckmann proposed to go back on the painstaking road of psychopathological differentiation in order to obtain the most homogeneous groups for investigation*"

First focusing on what differs rather than on what is common

In a "differentiated psychopathological" approach, the first step is to look for features that allow to "increase the distance" between groups of patients. This is what we referred to in the Dialogue's article (Foucher, Gawlik, Roth et al. 2020): *"[WKL] descriptions do not focus on what phenotypes have in 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*." It can be done by paying attention to rare signs and symptoms. A paradigmatic example is the classification of extrapyramidal diseases with the group of "Parkinson plus" syndromes and diseases which are poorly responsive to L-dopa. The different entities clinically differ on various rare clinical manifestations. For instance, a progressive supranuclear palsy (PSP) should be suspected when extrapyramidal symptoms are associated with a supranuclear palsy or backward falls, as shown in Table 1.

Remark: It is not that each manifestation taken independently is rare, but they are rarely occurring together: rarity is defined at the symptom-cluster level. Moreover, some labels might be too general. For instance, "cognitive impairments" are frequent. Yet the cognitive fluctuations of

Lewy body dementia (more or less associated with visual hallucinations) have little to do with the behavioral and cognitive changes of the FTDP -17.

Table 1

Parkinson + syndromes	Rare features indicative for
Dementia with Lewy bodies	Cognitive fluctuations Visual hallucinations (unmedicated)
Progressive supranuclear palsy (Steele-Richardson-Olszewski disease)	Supranuclear palsy Convergence insufficiency Backward falls Neck dystonia Cognitive impairment
Multiple system atrophy MSA-P: Striatonigral degeneration (SND) MSA-C: Olivopontocerebellar atrophy (OPCA) MSA-A: Shy–Drager syndrome	 (none) Cerebellar ataxia Autonomic dysfunction
Corticobasal degeneration	Alien hand syndrome Ideomotor apraxia
FTDP-17	Positive family history Personality changes Seizures

Table 1: Example of features that are rare in association with parkinsonism (bradykinesia, tremors, slow movement, muscle rigidity and postural instability) but the presence of which might be indicative for another degenerative disease. FTDP-17: Frontotemporal dementia and parkinsonism linked to chromosome 17. MSA are also illustrative for a primarily splitting approach that has been secondarily corrected by reverse phenotyping. MSA gathers three phenotypes that were formerly distinguished based clinicopathological correlations. They were considered to belong to the same disease process after the finding of the same histological biomarker: glial cytoplasmic inclusions (now known to be made of misfolded α-synuclein). Classically, the table is presented without the distinction between the three phenotypes. Yet from a WKL-perspective it is interesting to know about these distinctions as they are still relevant in clinical practice.

Increasing similarities between patients: giving sense and meaning

A less obvious aspect of a "differentiated psychopathology" approach is that it also aims at reducing the distance between cases that might differ on salient yet superficial features while converging on more fundamental characteristics. For instance, it is impossible to group patients suffering from multiple sclerosis on their mere clinical manifestations: one might have motor weakness in one limb, another electric-shock sensation in the body when moving the head, one might complain of tremor and lack of coordination, another from blurry vision… Here are the relevant features:

- Symptom-complexes arrangement according to white matter systematization: various localization syndromes indicative for a (focal) lesion of conduction pathways such as internuclear ophthalmoplegia.
- Clinical features suggestive of a demyelinating process. For instance, the conduction deficit is likely to be incomplete, e.g., blurred vision (rather than complete monocular blindness), muscle weakness (rather than complete paralysis). The deficit increases with the elevation of body temperature, i.e., Uhthoff's phenomenon. Clinical manifestations characteristic for an ephaptic conduction such as Lhermitte's sign, tingling sensations or paroxysmal kinesigenic choreoathetosis.
- A characteristic course of the symptoms that are said to be "separated in time and space." Separation in time means that clinical manifestations have a relapsing-remitting course (at least in the beginning – up to 85% of the cases). Separation in space means that symptoms vary in time, showing the involvement of at least two different brain regions.

Our purpose here is to show that similarities in appearance are frequently insufficient to gather the different casuistic into coherent phenotypes. Here the characteristic features of multiple sclerosis are not the phenomena themselves but their interpretation in meaningful symptom-complexes (localization syndromes) which course is characteristic. The variety of clinical manifestations is just too wide to be listed and it might miss some rare, yet highly indicative one such as a paroxysmal kinesigenic choreoathetosis.

Remark: In neurology, as for other branches of medicine, "syndrome" no longer means the mere grouping of symptoms as it is mostly used in psychiatry. Sure, this was its initial meaning,

but in current medical usage it comes with the implicit idea that there is a gathering principle behind it: the impairment of the same organ, tissue, region or system, such as the Bernard-Horner syndrome that suggests damage of the sympathetic trunk. For example, the latter could be integrated in a larger clinical picture such as one of the Pancoast-Tobias tumors.

We could use the term "***symptom-cluster***" to designate an empirically driven symptom-grouping which has not been already "validated" by finding the cause for this gathering.

Sometime the above concepts (syndromes and symptom-cluster) are confused with the concept of symptom-***dimensions*** as found using factorial analysis. Yet, the former ascribes to the ***naturalistic framework*** (one cause of major effect) while the latter ascribes to the ***normativistic framework*** (the addition of multiple - non-interacting - causes of minor effects). Symptom-clusters suggest the existence of categories, i.e., entities of different essence. Dimensions suggest, for example, that there is no difference between patients and controls except a departure from the norm on dimensions such as disorganization and positive symptoms.

Should we fear instilling a bit of theory into observations?

It might be impossible to find a relevant common feature without some theory; in other words, without interpreting the casuistic. In the above example of the PSP, we implicitly used the theory-laden interpretations:

- Neurological systematization: supranuclear palsy and backward falls do not map on substantia nigra or the basal ganglia and suggest the degeneration of other systems.
- Neurological localization syndromes: supranuclear palsy and backward falls are known to occur together in case of mesencephalic damage.

This means that we might consider some features more important than others, while nonobvious ones will be actively looked for to see if they fit with the expected pattern etc.

We are no longer accustomed to interpreting clinical pictures. An optimistic reason could be that current diagnostic tools made us used to the symptom-checklists practice. Yet a more pessimistic account for the discrepancy between medical and psychiatric clinical practice might be that interpretations still are explicitly discouraged by the endorsement of an ***a-theoretic*** metatheory. This atheoretic stance stems from Carl Hempel's lecture at the Work Conference on Field Studies in the Mental Disorders (Hempel, 1961). As a leader of logical positivism (or neo-positivism), he stated that "knowledge of true value could solely be given by direct empirical

observations devoid of theoretical imprint." Yet the critiques precisely raised against this atheoretical prescription precipitated the fall of logical positivism and in the mid-1960s neopositivism was "dead, or as dead as a philosophical movement ever becomes" (Passmore, 1967). However, its most criticized stance still rules current consensus classifications (DSM-5 and ICD-11) and remains a widely accepted methodological metatheory in psychiatry research.

The "symptom-complex" methodology

Conversely, the WKL research program kept on with the medical practice of interpreting clinical presentations by using the concept of "symptom-complex." A symptom-complex is not merely a symptom-cluster, i.e., the above chance co-occurrence of different manifestations. A symptom-complex has an intrinsic logic. Clinical signs and symptoms are causally arranged: the core pathology can be inferred from elementary symptoms which can trigger other manifestations. This arrangement was later renamed as primary and secondary symptoms by Eugen Bleuler (1911). For example, a disturbance of psychomotor systems could be responsible for parakinesia (primary) which could itself be responsible for a mismatch between expected and actual reafferences that the patient experiences (or interprets) as an external influence (secondary passivity phenomenon).

Phenotypical theories

Beyond this symptom-complex heuristic which allows giving sense to the clinical pictures, other WKL "heuristics" helped in the description of phenotypes. In the main paper, we mentioned the longitudinal heuristic (as for multiple sclerosis) and the family aggregation heuristic. We shall address Hector Warnes's comment related to the "prognostic heuristic" in another response.

Lumpers *vs* splitters: aren't we splitting too much?

Karl Jaspers (1946) considered Wernicke's (1906) psychopathology to be too atomistic, resulting in too many different symptom-complexes. Considering that Kleist and Leonhard mostly kept on with this "splitter" approach, the "final" classification might also appear too differentiated: 35 major phenotypes plus 36 minor ones.

The various interpretation of the principle of parsimony

Most of us might agree that the principle of parsimony should apply and that within an equally adequate account of natural phenomena, the simplest one should be preferred.

(Importantly, the principle of parsimony should not be considered to be a logical principle [in the formal sense]). It is a pragmatic principle which may or may not be right.

Yet even if the WKL approach is not more adequate than the DSM one, there are different ways to evaluate simplicity. Let us illustrate this using the DSM definition of major depressive disorders (MDD):

- If we accept the DSM check-list logic, sure that the DSM-5 account of MDD is simpler than the 20 WKL-phenotypes that can overlap with it, one DSM-MDD is simpler than 20 WKL-phenotypes.
- But if we specify all possible combinations of the 2+7 DSM-5 items for MDD, the result is 227 possibilities: $[C_1^2 \cdot C_{4\to7}^7] + [C_2^2 \cdot C_{3\to7}^7] = 227$ (with $C_{4\to7}^7 = C_4^7 + C_5^7 + C_6^7 + C_7^7$). In which case 20 WKL-phenotypes are a simpler account relative to the 227 variants of the same DSM-5 MDD.

Increasing homogeneity rather than relying on large numbers

But beyond the principle of parsimony, a splitting approach might also enhance our chance to find biological correlates if a common condition is accounted for by rare diseases (the question of "rarity" of diseases will be addressed independently). Neurologists prefer to define highly differentiated phenotypes, even if they are too much differentiate. While reducing the sample size, this splitting approach also increases homogeneity within the group so that even rare causes can be found. A nice example is provided by the finding of the DYT1 gene in dystonia. The gene could only be isolated from the genetic analysis of a small sample of the rarest and most severe forms of dystonia, i.e., generalized dystonia (~20% of patients) (Lebre, Durr, Jedynak et al. 1999). This would have been impossible to do from a larger but less homogeneous sample as the signal would have been hidden by the noise. Yet, once this major cause has been isolated, the phenomenological variants of the disease can be described by a reverse phenotyping approach (Gasser, Windgassen, Bereznai et al. 1998). The WKL frramework follows quite similar reasoning so that it is acceptable to be too atomistic if it allows to concentrate specific diseases in samples, even if it means having to redefine the phenotypical expression once the cause is known.

Conclusion

From a philosophy of science perspective, it could be said that "differentiated psychopathology" is one of the methodological metatheories of the WKL naturalistic framework. It is a double movement of increasing the distance between dissimilar cases and reducing the distance between similar ones (Figure 1). It has more to do with the neurologists splitting approach (with secondary reverse phenotyping) than with the dominant lumping approach in psychiatry which is considered to lower the signal/noise ratio by mixing up too many different entities.

Figure 1

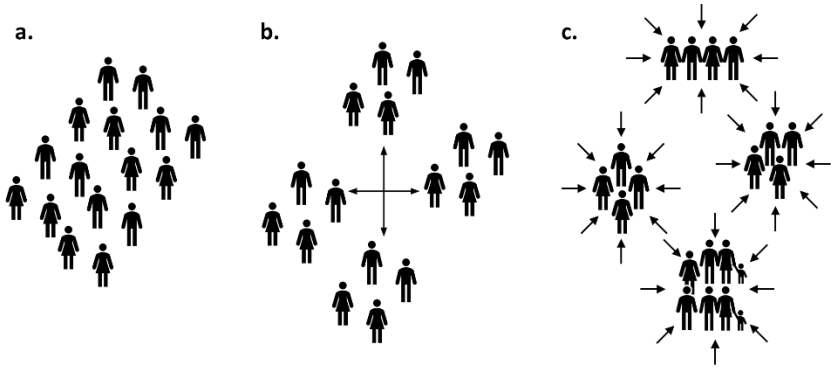

Figure 1: The double movement of the "differentiated psychopathology" approach. Starting from a group of patients (a), it attempts to increase the distance between dissimilar cases (b) and to reducing the distance between similar cases, e.g., a contextual feature of familiality as illustrated in the bottom group (c).

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May 13, 2021