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POINTS OF VIEW/FORMULATION

Hermann M. van Praag

Kraepelin, biological psychiatry, and beyond

Abstract One of Kraepelin's major contributions has been the introduction of the nosological principle in psychiatry. Mental pathology, he presumed, is subdividable in discrete entities each based on a specific pathophysiology. Kraepelin provided the diagnostic process in psychiatry with a solid infrastructure. It has been used in biological psychiatric research until this very day. Searching for the biological determinants of categorical entities has been its major goal. The yield of those efforts has been meagre, in that none of the biological findings reported so far seemed to be specific for a particular nosological entity. The question thus arises: is nosology the right model to classify mental disorders. It is suggested that it is not. The disease categories presently delineated are utterly heterogeneous, and therefore cannot be expected to have a well-defined pathophysiology. The nosological system cannot be rejected (as yet), but it has to be upgraded by incorporation of a strong dynamic-functional component. The functional components should become the focus of biological psychiatric research. The question whether an alternative classificatory model, such as the reaction form model, has to be preferred in biological psychiatry should become a matter of serious discussion.

Key words functional psychopathology · nosological classifcation · DSM validity · biological psychiatry · specificity biological varieties

Kraepelin and biological psychiatry

Kraepelin made fundamental contributions to psychiatric diagnosing. Out of the diagnostic chaos that prevailed in psychiatry during the nineteenth century, he was able to curve out two pathological conditions he considered to be disease entities: dementia praecox (later called schizophrenia) and manic-depressive disorder. His work was based on systematic longitudinal observations and as such it introduced scientific methodology in psychiatry.

Moreover, he inaugurated a new diagnostic paradigm in the realm of mental disorders, that of the nosological entity. Mental pathology, Kraepelin proposed, could be divided in discrete disorders, distinguishable one from the other. Each with its own symptomatology and course; each with its own specific pathophysiology. Nosology, according to Kraepelin should be the principal guideline in exploring the biological roots of mental pathology.

And so it came to be. The influence of his ideas has been enormous, until this very day. Schizophrenia and (unipolar and bipolar) depression are major foci of biological psychiatric research. Most biological psychiatric research, moreover, is predicated upon the nosological presupposition; aspires to elucidate the biological underpinnings of discrete disease "packages" as presently defined by the DSM system, a classification system that heavily leans on Kraepelinean idea's.

The question I want to raise is, whether the guidelines Kraepelin proposed have indeed been productive for biological psychiatry, or rather hampered progress in this field.

Kraepelin and biological schizophrenia research

Starting point of my reasoning is, that refined diagnosing is the very bedrock of biological psychiatry: precise definition of the psychopathological construct the pathophysiology of which one wants to elucidate. The question to be addressed can thus be specified as follows. First, do the Kraepelinean constructs schizophrenia and depression meet the clarity criterion. Second, is nosology the proper foundation for biological psychiatric research.

em. Prof. Dr. H.M. van Praag (✉)
Center for Public Mental Health
Dept. of Psychiatry and Neuropsychology
University of Maastricht
P.O. Box 616
6200 Maastricht, The Netherlands
E-Mail: h.m.van.praag@vanpraag.com

First the construct schizophrenia (as presently defined by the DSM system) as to its diagnostic acuity. Does that construct indicates/predicts a specific symptomatology. It does not. The patient shows psychotic features, such as hallucinations, delusions, confusion and disorientation but in a variety of combinations. The non-psychotic symptomatology is as varied and unpredictable as the psychotic symptoms are.

A subjective criterion, such as Rümke's "praecox gefühl", referring to difficulties in establishing an emotional relationship with the patient, appeared not to be specific, hard to verify, and strongly dependent on the interviewer's ability to open up the patient.

Does the diagnosis schizophrenia predict course and prognosis of the disorder? It does not. Psychotic episodes may appear gradually or rather suddenly. They may be short-lived or protracted, up to chronicity. The patient may improve substantially, certain symptoms may last, or he may regress into a chronic psychotic state. The patient may become professionally active again or may remain disabled. In other words, course and prognosis are uncertain and hard to predict.

The premorbid way of living and the premorbid personality structure may be disturbed from childhood on, or rather inconspicuous until shortly before the outbreak of the psychosis.

Several biological systems have been found to be in disorder; foremost the dopaminergic system, but several others as well, such as the serotonergic and the glutaminergic system. Sofar, however, none of the findings in question are pathognomonic for schizophrenia, or a well-defined subgroup of schizophrenics. Most of those disturbances, moreover, have been observed in other diagnostic categories as well.

Recently various genes have received the qualification: (possible) schizophrenia genes [1, 3, 8]. That label, however, is much to assuming. That of (possible) psychosis genes would be the more appropriate. Specificity for schizophrenia or a particular subgroup of schizophrenia has not been demonstrated [2].

Treatment response, finally, is unpredictable. Some patients diagnosed as schizophrenics respond excellently to psychotropic drugs, some reasonably well, others poorly, some not at all.

One can thus hardly avoid the conclusion that the precision and clarity of the diagnosis schizophrenia leaves much to be desired, and that the predictive validity of that construct is close to nil. The diagnosis schizophrenia as it is used today is almost synonymous with that of psychosis. Studying the pathophysiology of a construct of such heterogeneity is bound to fail and surely it has failed. We are not much closer to its biological roots than we were several decades ago. That outcome was predictable (and I predicted it already in 1976 in a paper called "The impossible concept of schizophrenia"). What would one expect from a research program into the pathophysiology of, say, cardiac disorders. Little if anything. The diagnosis schizophrenia I consider of comparable exactitude. The chance that utterly heterogeneous psychopathologial constructs will be produced by well-defined brain disturbances is negligibly small.

Kraepelin and biological depression research

Much the same as was discussed regarding schizophrenia holds true for depression.

Symptomatologically, mood lowering is its anchor symptom, but for the rest the symptoms vary considerably. In other words the term depression covers a variety of syndromes. Moreover, these syndromes appear more often than not in conjunction with other mental disorders, in particular with anxiety- and personality disorders. Depression without further specification is a diagnosis as general and thus as vague as, for instance, that of anaemia. It gives some information about someone's mental condition, but far too little.

Course and prognosis of depression are unpredictable. It may start rather suddenly, sometimes even overnight, or gradually, in the course of weeks or months. It may last for a few days, up to many months or even years; recurring frequently, with large time intervals or (more seldom) not at all. The symptoms of depression may be hardly noticeable to the outer world, may cripple the patient both socially and professionally or may even reach psychotic degree. Recovery may be full, partial—by which the patient remains hampered in his daily activities—or the disorder may take a chronic course.

The premorbid personality structure as well as the living circumstances may be clearly disturbed, showing, for instance, considerable weaknesses in interpersonal skills and adaptability to changing living conditions, or may be quite undisturbed leaving relatives and friends of the patient wondering how on earth this person could become depressed.

The depression may follow psychotraumatic life events, or may occur "out of the blue", without any discernable provocation.

A variety of neurobiological disturbances have been reported to occur in depression. Most prominently in the monoaminergic systems, the stress hormone system, and in the production of some growth factors, such as BDNF. For instance, the concentration of 5-hydroxyindoleacetic acid in cerebrospinal fluid was found to be diminished, the density of serotonin 1A receptors in the brain to be decreased and the synthesis rate of serotonin to be diminished; all signs of disturbed serotonergic functioning in the brain (Review: [7]). These disturbances, however, are found in some depressive patients, not in all, and are not specific for depression, found as they are in other diagnostic categories as well.

Response to treatment, biological or psychological in nature, is hard to predict. Patients may become symptom-free, show residual symptoms or do respond hardly if at all.

Half a century of intensive research has not elucidated the biology of depression. This was to be expected. Again, it is unlikely that insufficiently specified diagnostic constructs will turn out to be caused by specific, well-definable pathological processes.

Beyond kraepelin

These observations and considerations convinced me that biological psychiatric research has been and still is proceeding in a dead end, a street called: nosological alley. I feel, and have felt for most of my professional life, that the diagnostic process in psychiatry should change direction, in particular if the goal is to explore the biological underpinnings of mental pathology. Two strategies, I proposed, should direct that effort. I have named them verticalization and functionalization [6, 7]. Only the first approach I bring to bear. In brief, functionalization implies that diagnosing in psychiatry should proceed stepwise.

First the diagnostic grouping to which the disorder belongs should be determined. That is, a categorical diagnosis should be made. For instance, the mental state in question is considered to belong to the basin of schizophrenic disorders. This first diagnostic step provides no more than a global diagnostic indication. It is no more informative than the statement that a given person complaining of pain in the chest is probably suffering from a cardiac disorder. Diagnostic basins are by definition heterogeneous.

Next the syndrome is defined. Also this diagnostic information is far from precise. Syndromes often appear in incomplete form and many patients suffer simultaneously from more than one complete or incomplete syndromes.

Hence a third diagnostic step seems to me crucial. One I have called functionalization of diagnosis. Functionalization means, defining first of all the psychopathological symptoms constituting the syndrome and next—most importantly—examine and if possible measure the psychological dysfunctions underlying the psychopathological symptoms. Psychopathological symptoms and psychic dysfunctions are not synonymous. The psychopathological symptom is the way the psychic dysfunction is experienced by the patient and observed by the investigator.

The last step I consider to be quintessential. If no methods are available to measure the assumed dysfunctions, they should be developed. Functionalization of psychiatric diagnosing, thus, presupposes close collaboration between psychiatrists and experimental clinical psychologists.

A few examples. In case of dementia symptoms, the underlying cognitive disturbances should be tracked and measured. In case of hallucinations the same applies to the underlying perceptual disturbances. In case of anhedonia the defect in linking a particular perception with the corresponding emotion should be searched for.

Psychological dysfunctions underlying psychopathological symptoms should be, I propose, the focus of biological psychiatric research. It seems much more likely that brain dysfunctions correspond with disturbances in psychological regulatory systems than with largely man—designed categorical entities, or with symptom complexes rather arbitrarily designated as a syndrome.

The search for biological determinants of psychological dysfunctions has indeed been proven to be much more fruitful than the search for the biological cause of a particular nosological entity, such as depression or schizophrenia (For review see [7]).

Functionalization of diagnosis will result in scientification of psychiatric diagnosis

Functionalization, will make psychiatric diagnosing more precise, more scientific, and more attuned to goal-directed biological studies and focused therapeutic interventions.

More precise and more scientific, because psychic dysfunctions are much better measurable than disease categories and syndromes, often even quantitavely.

Secondly, this approach provides the diagnostician with a detailed chart of those psychic domains that function abnormally and those functioning within normal limits. Ultimately this approach will lead to what I have called a psychiatric physiology, a detailed chart of brain dysfunctions underlying abnormally functioning psychological regulatory systems.

Treatment, too, could benefit from this approach. Drug treatment as well as psychotherapy are presently pretty much unfocused. We prescribe drugs because someone is psychotic, depressed, anxious or otherwise out of balance. Any further specification is generally lacking or deemed to be unnecessary. This is not the way to further psychopharmacological research, nor the way to increase the chance of finding new, innovative, and psychopathologically more specific psychotropic drugs.

The same reasoning holds for psychological treatment. We may recommend psychotherapy. For what exactly, is seldomly clear. What will be its focus? What do we hope to achieve? It is rarely defined in any detail. This holds in particular for psychodynamically oriented psychotherapies. Cognitive-behavioral therapists do some what better in this respect. Functionalization of diagnosis would make systematic detailing of therapeutic goals feasible. In fact it would be its logical consequence.

The post-kraepelinean approach in practice

Our own research is a case in point. From the fifties on, we have studied the biology of depression, focusing mainly on monoaminergic systems.

First our focus has been a nosological construct, i.e. melancholia. It turned out to be the wrong focus. The construct seemed to be utterly heterogeneous; that is: few patients showed "pure" melancholia. The data we produced were confusing. We found in this group, amongst other things, disturbances in the serotonin system. On the average, the depressed group differed in this respect from the control group. However, such aberrations occurred in an unpredictable way, demonstrable as they were in some patients but not in others.

Next, we focused on a particular syndrome, the so-called syndrome of vital depression. This focus proved to be unsatisfactory as well, and for much the same reasons. Pure vital depression appeared to be rare. Most patients showed only parts of that syndrome, and often in conjunction with (parts of) other syndromes. Again we observed serotonin disturbances, but, as before, in some patients, not in others.

Those were the reasons that prompted the development of the functionalization concept. We decided to dissect the syndrome in its component parts—i.e. the psychopathological symptoms—and next to study the underlying psychic dysfunctions and then to search for relationships between psychological and biological dysfunctions.

This turned out to be a productive approach. The serotonin disturbances seemed indeed to correlate with psychic dysfunctions, i.e. with disturbances in anxiety- and aggression regulation. Those relationships, moreover, appeared not to be limited to depression but were also demonstrable in other diagnostic categories. They turned out to be functionally specific, i.e. to be linked to disturbances in psychic regulatory systems, not categorically or syndromally specific. They exist independent of nosological or syndromal diagnosis.

The functional approach led thus to specific brain/behavior relationships. The nosological and syndromal approach did not.

Kraepelijn and biological psychiatry: an interim balance

Kraepelin is considered to be the father of a scientifically oriented psychiatry, and rightly so. His basic diagnostic model was based on nosology: the idea that mental pathology is subdividable in discrete disease entities, each with their own pathophysiology. It gave biological psychiatry a clear headstart, directed as it should be on the brain disturbances presumed to underly the categorical entities he had carved out.

This model, however, proved to be unsatisfactory. Those categories and most of the ones later proposed by the DSM system proved to be heterogeneous, in almost, all respects. Heterogeneous psychopathological constructs cannot be expected to be based on well-defined neurobiological processes. Practice confirmed theory. Fifty years of intensive research has, it is true, brought to light a plethora of interesting brain disturbances, but none of them seems to be specific for any of the given disease categories.

It is my firm conviction that the rigid nosological approach has had its time, particularly in biological psychiatry. It has to retreat in favour of a dynamic-functional disease concept. Not the largely man-made nosological entity should be its focus, neither the syndrome so often capricious in its symptomatological composition, but the psychic dysfunctions underlying the psychopathology, being in fact its generator. This approach will lead, I assume, to accelerated scientification of psychiatric diagnosis and to a greater yield of biologic psychiatric research.

I have not touched upon a basic question underlying this whole reasoning. Is mental pathology indeed subdividable in discrete entities, in definable "packages"? Is nosology a valid classificatory model in psychiatry? Or should we think (again) of an alternative model, in particular the reaction-form model. I think we should, but space constraints prevent me from discussing it here. I did so elsewhere [5].

In conclusion, then, Kraepelin's merits for psychiatric diagnosing can hardly be overestimated. Having said that, I add that no model holds forever. That's true for diagnostic models as well. Every model, thus, should be periodically weighted, evaluated as to its usefulness. So also the nosological model. Kraepelin, I think, given his intellectual stature, would have been the first to admit that.

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