

In Debate

Disease Versus Dimension in Diagnosis

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The Argument for Disease

It is chimerical to think that psychiatric illness can be collapsed into a couple of smooth dimensions. This is a conceit that comes to us from psychoanalysis, which was uninterested in specificity of treatment. In reality, just as there are discrete diseases of the kidney, there are discrete diseases of the brain that produce behavioural symptoms. These can no more be scaled than renal tuberculosis and renal carcinoma can be arrayed onto a single dimension.

Let us consider the view, articulated by Samuel Guze¹ in 1992, that psychiatry is a branch of medicine. If we are to regard psychiatric diagnoses as medical diagnoses, how might they be constructed? Building on Guze,¹ Max Fink and Michael Alan Taylor² have proposed a 3-fold basis for carving out discrete psychiatric illnesses: describing an illness entity in well-circumscribed psychopathologic terms; verifying its existence with laboratory measures; and, validating it with a distinctive response to treatment. Based on this triune measure of what one might call disease-ness, what solid disease diagnoses does psychiatry possess?

Melancholia

Out of the soup of depression, it is possible to fish several solid diagnoses that fulfill the above criteria. The major depression of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) is a nondisease and should be divided into melancholia and nonmelancholia.³ Nonmelancholia is anything but a discrete disease entity, while melancholia is probably the most solid disease that psychiatry possesses, characterized, in psychopathological terms, by psychomotor change and profound neurovegetative disturbances, and verified by such biological markers as a positive response to the dexamethasone suppression test (in contrast to nonmelancholia), by REM latency, and by a

blunted thyroid-stimulating hormone response to exogenous thyrotropin-releasing hormone.⁴ Finally, melancholia is validated by a distinctive response to tricyclic antidepressants (TCAs) and to electroconvulsive therapy (ECT). Not all patients with purported melancholia will display these biological markers, but it is profoundly interesting that within the melancholia diagnosis there is a psychopathological core of patients possessing this biological homogeneity. (Atypical depression neither shows the typical neurovegetative signs of melancholia nor responds well to ECT.) These cases of melancholia cannot be arrayed on a dimensional scale, except in the trivial sense that the disease waxes and wanes.

Catatonia

Formerly, catatonia was considered a subtype of schizophrenia. DSM-IV conceded that “catatonic features”^{5, p 417} might characterize a mood disorder as well. Seldom has catatonia been seen as an independent illness entity worthy of “a home of its own,” as Fink and Taylor⁶ put it (in the title of their article). Nevertheless, clearly it belongs on the list of genuine psychiatric diseases because its psychopathology is well specified and has a rating scale of its own. To be sure, it does not possess a biological marker (verification), but in intravenous lorazepam, catatonia possesses a differential treatment response (validation). (No other psychotic illness responds to lorazepam; symptoms of catatonia are also relieved with ECT.) Catatonia has no dimensional features: the diagnosis is made with the presence of 2 or more signs, and the score on the catatonia rating scale does not influence the response to treatment. It would be incorrect to say, as the dimensional argument might put it, that all of us possess embryonic catatonic symptoms that then aggravate under stress.

Atypical Depression

Atypical depression is less clearly delineated than melancholia and catatonia, in psychopathological terms, but nonetheless displays some underlying biological unity. William Sargant’s students coined the term in 1959,⁷ which was later revived to mean, somewhat differently, depressions characterized by hypersomnia, hyperphagia, leaden fatigue,

and a high sensitivity to emotional rejection. About verification, there is no biological marker such as the dexamethasone test (DST) for atypical depression, but in terms of validation it does seem to respond differentially to monoamine oxidase inhibitors. Atypical depression does not appear to be dimensional but represents an illness condition *sui generis*.

Attention-Deficit Hyperactivity Disorder

Many patients diagnosed with attention-deficit hyperactivity disorder (ADHD) in the current epidemic of the disorder have little in common biologically with the core of true cases of ADHD. Nevertheless, unquestionably ADHD represents a unitary clinical syndrome with an underlying biology of its own about dysrhythmic electroencephalogram (EEG) (verification) and differential response to amphetamine (validation). One fishes up from the pediatric soup as well some other diagnoses, such as conduct disorder, that lack a clear biological substrate. These are often linked to ADHD, to a point where some observers believe there is only one so-called bad boy pediatric behavioural syndrome. Nonetheless, let us not lose track of ADHD having a distinctive biological core.

Panic

Harvard psychiatrists Stanley Cobb and Mandel Cohen⁸ originally established in 1940 that a carbon dioxide challenge would precipitate an acute episode in chronic anxiety patients, but not in control subjects. In 1967, Ferris Pitts and James McClure⁹ at Washington University confirmed that an infusion of lactate would provoke anxiety attacks in patients with anxiety neurosis. About psychopathology, it is difficult to differentiate panic from other anxiety pictures. Nevertheless, panic does seem to have a biological substrate that other forms of anxiety lack (verification through panicogens), and a distinctive response to TCAs that other forms of anxiety do not possess (validation). Therefore, panic qualifies as a disease of its own.

And that is it. Those are the disease entities in psychiatry that, to date, have been relatively well characterized. Others will doubtless follow as the concept of biological markers again gains traction (after the premature discarding of the DST).

Nonetheless, we have not finished the list of DSM-style disorders. Perhaps there is hope for dimensional approaches in some of the others? Elsewhere in the brew are such illness concepts as bipolar disorder (BD), schizophrenia, and schizoaffective disorder. Perhaps they are dimensional in nature? Nevertheless, a more urgent question is: Do they exist, or are they nosological artifacts?

The poster child for the dimensional notion is the bipolar spectrum.¹⁰ However, there is a basic problem in calling anything bipolar; it is a usage that makes polarity the chief nosological characteristic. The term bipolar assumes, in the absence of convincing evidence, that unipolar depression is a quite different entity than bipolar depression. Nevertheless, this assumption of 2 very different depressions defies both good judgment and clinical science. It is well known that any

chronic depressive illness may sooner or later throw off a manic episode. Does this therefore change the diagnosis completely? BD is one of the oldest illness concepts in psychiatry, going back to Emil Kraepelin's manic depressive illness (MDI) in 1899.¹¹ Nevertheless, Kraepelin understood under the concept of MDI virtually all depressions, plus mania. He did not carve out a separate unipolar depression. It was only the German nosologist Karl Leonhard¹² who, in 1957, gave wings to the bipolar notion.

Recently, bipolarity has attracted a great following. BD II is commonly diagnosed in children who kick the sofa, and BD III in hypomania emerges following the administration of an antidepressant. The whole bipolar spectrum has become a wand to conjure with.¹³ Nevertheless, one is left with the feeling that this association somehow represents a triumph of pharmaceutical merchandizing rather than science. The bipolar spectrum has no distinctive psychopathological picture, no biology of its own, and no distinctive response to treatment. By the triune criteria laid out above, it qualifies with difficulty as a single disorder. Therefore, BD, eminently dimensional, may turn out to be a puff of smoke.¹⁴

Since the days of psychoanalysis, schizophrenia has served as a poster child for the concept of dimensionality. What the analysts could not understand, or deal with, they called schizophrenia. There is no biological marker for schizophrenia as a whole, although in neuroimaging and histological pathology there are findings aplenty. However, none of them are generalizable to people with schizophrenia as a group. There is no distinctive schizophrenia psychopathology, and the tryptic picture of positive symptoms, thought disorder, and negative symptoms may or may not be present. Nor is there a single biological marker for schizophrenia, although here again, some clinically ill-defined groups of patients present findings, others do not. By psychopathological standards, verification by biological marker, and validation by response to treatment, schizophrenia fails as a disease. It makes much more sense to place schizoaffective disorder, classical schizophrenia, and schizotypal personality in a market basket called chronic psychosis and to say that it is not necessarily more severe than nonpsychotic illness, but is different.

What is left of the notion of dimensionality? One philosophical problem remains for the dimensionalists: after a certain point, changes in quantity become changes in quality. If there are sharp differences in intensity, are we perhaps dealing with 2 different illnesses? For example, one takes the difference between anxiety and what the Europeans call anguish, the latter having a heavy component of physical symptoms. The great Spanish nosologist Juan J Lopez-Ibor¹⁵ referred to anguish as anxious thymopathy, treatable with acetylcholine, as opposed to mental anxiety treated with psychoanalysis. We have already reviewed the distinction between melancholia and nonmelancholia, disorders that represent not merely dimensional differences but diseases as unlike as measles and tuberculosis.

It is true that there are illness conditions that display significant differences in intensity while not changing in kind, thus true examples of dimensionality. But there are not many. Chief among those that may be scaled rather than compartmentalized are the so-called personality disorders, a holdover from psychoanalysis. The present system of dividing personality disturbances into many watertight units, as though we were classifying measles and mumps, does not withstand the test of evidence. Most of the supposedly discrete disorders overlap; patients who are candidates for one are frequently candidates for all, and it makes more sense to think of personalities as being mildly, moderately, and severely disordered without specifying particular illnesses.

Today, when all minds are turned to the preparation of DSM-V, the question of dimensionality has asserted itself with greater insistence as a possible new principle for the classification of illness. This insistence must be rejected. The drafters of DSM-III flirted with dimensionality in 1976 in the diagnosis of mood disorders. They ended up rejecting it, although what they finally came up with was scarcely more satisfactory. Dimensionality should keep its distance from DSM-V as well.¹⁶

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Edward Shorter

Functionalization of Psychiatric Diagnosis

Kraepelin introduced 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. According to Kraepelin, nosology should be the principal guideline in exploring the biological roots of mental pathology.

Against Nosology

And so it came to be. The influence of his ideas has been enormous, until this day. Most biological psychiatric research is predicated on the nosological presupposition, and aspires to elucidate the biological underpinnings of discrete disease packages as currently defined by the DSM system, a classification system that heavily leans on Kraepelinian ideas.

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

The starting point of my reasoning is that refined diagnosing is the bedrock of biological psychiatry; it is the precise definition of the psychopathological construct, the pathophysiology, of which one wants to elucidate. The questions to be addressed can thus be specified as follows. First, do current diagnostic constructs meet the clarity criterion? Second, is nosology the proper foundation for biological psychiatric research? I take the construct of schizophrenia as an example.

Does that construct indicate and (or) predict a specific symptomatology? It does not. The patient shows psychotic features, such as hallucinations, delusions, confusion, and disorientation but in various combinations. The nonpsychotic symptomatology is as varied and unpredictable as the psychotic symptoms. A subjective criterion, such as Rümke’s “*praecox gefühl* [feeling],”^{1, p 435–437} referring to difficulties in establishing an emotional relationship with a 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 of 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. A patient may improve substantially, certain symptoms may last, or a patient may regress into a chronic psychotic state. A 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. However, so far, none of the findings in question are pathognomonic for schizophrenia, or a well-defined subgroup of people with schizophrenia. Moreover, most disturbances have been observed in other diagnostic categories as well.

Recently, various genes have received the qualification: (possible) schizophrenia genes.²⁻⁴ However, that label is much too assuming. That of (possible) psychosis genes would be the more appropriate. Specificity for schizophrenia or a particular subgroup of schizophrenia has not been demonstrated.⁵

Finally, treatment response is unpredictable. Some patients diagnosed with schizophrenia respond excellently to psychotropic drugs, some reasonably well, others poorly, and some not at all.

Thus one can hardly avoid the conclusion that the precision and clarity of the schizophrenia diagnosis leaves much to be desired, and that the predictive validity of that construct is close to nil. The diagnosis of schizophrenia as it is currently used 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 in 1976, in a paper entitled "The Impossible Concept of Schizophrenia"⁶). What would one expect from a research program into the pathophysiology of, say, cardiac disorders? Little if anything. The diagnosis of schizophrenia I consider of comparable exactitude. The chance that utterly heterogeneous psychopathological constructs will be produced by well-defined brain disturbances is negligibly small.

For Functionalization

These and similar observations 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. The strategy proposed to direct that effort I called functionalization.⁷⁻⁹ This process 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.

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 crucial to me. One I have called functionalization of diagnosis. Functionalization means defining, first of all, the psychopathological symptoms constituting the syndrome, and then—most importantly—examining and, if possible, measuring the psychological dysfunctions underlying the psychopathological symptoms. Psychopathological symptoms and psychic dysfunctions are not synonyms. 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.

A few examples. In the case of dementia symptoms, the underlying cognitive disturbances should be tracked and measured. In the case of hallucinations, the same applies to the underlying perceptual disturbances. In the 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.⁸

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 quantitatively.

Second, 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 currently 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 seldom 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-behavioural therapists do somewhat better in this respect. Functionalization of diagnosis would make systematic detailing of therapeutic goals feasible. In fact it would be its logical consequence.

In conclusion, Kraepelin's merits for psychiatric diagnosing can hardly be overestimated. Having said that, I add that no model holds forever. That is true for diagnostic models as well. Thus every model should be periodically weighted, evaluated as to its usefulness, so also the nosological model. In my view, it is practically handy, but scientifically unusable.

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Herman M van Praag

Rebuttals

Disease Versus Dimension in Diagnosis: Response to Dr van Praag

Casting this exchange as a debate will arouse unrealistic expectations in readers looking for a tractor-pull because I agree with almost everything Dr van Praag has said.

He forcefully makes the case that there is no such thing as schizophrenia and I certainly agree. There is no biological marker for it, no fixed prognosis, no predictable response to treatment, no single pathognomonic symptom. Kraepelin identified a core of illness with a progressive downhill course. The disorder that he identified began in the young and ended reliably in dementia. Hence Kraepelin's dementia praecox.

Since Kraepelin, the boundaries of this illness have been vastly expanded so that, as Dr van Praag remarks, schizophrenia is coterminous with psychosis. Indeed, we should just call it chronic psychosis and end the pretense that we are dealing with a fixed disease entity such as mumps.

Kraepelin was actually not the first to divide psychiatric psychopathology into fixed diseases, but the system that he codified has largely stood the test of time. Indeed, there might be valid reasons to return to his MDI in the diagnosis of serious mood disorders, ending the fiction that BD is an entity very different from unipolar disorder. Dr van Praag concedes that there are big disease basins and of course he is right. There is a psychosis basin, a mood basin, a dementia basin, and so on.

Dr van Praag challenges the validity with which we have constructed separate syndromes within these basins. Here again, he is largely right. Many of the DSM syndromes simply do not hang together, as they are almost random aggregations of individual symptoms. Major depression is a case in point: a so-called syndrome that could easily be disaggregated, its contents dispatched to other syndromes. In constructing syndromes, it would be wonderful if we could use biological markers to guide us, and indeed to some extent we can, as I pointed out in my original essay. The point is that the construction of reliable syndromes is possible if one is willing to go beyond the phenomenology of the current clinical picture and be guided by previous response to treatment, family history, and other characteristics that the current DSM system ignores. Dr van Praag does not dilate on biological markers, but I have the feeling that he would not disagree with the above.

Against nosology? Meaning against the classification of illness? Let us not get carried away. Nevertheless, Dr van Praag's remarks about functionalization have a long and distinguished history in the German tradition of psychopathology. Blocked by psychoanalysis, it never successfully crossed the ocean. German émigrés such as Fritz Freyhan¹ attempted to carry on this tradition in North America with the doctrine of target symptoms, but gained little traction, as the differential responsiveness to medications of psychopharmacology seemed to take place at the disease and syndromic levels, rather than only at the target-symptom level.

Does functionalization mean we should abandon the disease-basin and syndrome approaches? Probably not. But I did not see the word continuum in his essay, and he is talking about something quite different.

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Edward Shorter

Does Psychiatry Really Know “Solid Disease Diagnoses”?

I partly agree, partly disagree with Dr Shorter’s argument. Dr Shorter considers melancholia “the most solid disease that psychiatry possesses.”

Is melancholia indeed an illness entity described “in well-circumscribed psychopathologic terms”? Yes, on paper it is, but I add several important practical caveats. First, according to our own research, few patients meet all the required criteria. Second, several of the required symptoms are by no means specific for melancholia, occur in various other psychiatric states as well. Third, the overlap with other psychiatric syndromes is more than considerable. Pure melancholia is very rare. These observations detract from its proposed status as a “solid psychiatric disease.”

Is this diagnosis verifiable by laboratory measures? I do not think so. I know of no test specific for melancholia. Indeed, many biological processes have been found in disorder in melancholia, but no one is specific for that disorder, and none is found in all, or even most, patients carrying that diagnosis.

Is the diagnosis melancholia validated by a distinctive response to treatment? It is not. ECT can certainly exert a profound therapeutic effect, but by no means in all patients. A not inconsiderable proportion does not respond, respond only partly, or respond temporarily.

The disease-ness of melancholia is, I believe, insufficient to serve as useful focus of neurobiological research. No wonder 60 years of searching for its biological roots did not provide clearcut and reproducible answers.

What is true for melancholia is even more true for almost all other psychiatric diagnoses. Diagnosing on a strictly categorical basis has not provided psychiatry with discrete, “solid disease” entities.

A second objection. I do not consider psychiatric disorders, straightforwardly, as “diseases of the brain.” Certainly, psychiatric disorders presuppose disordered brains. Without a brain, no (abnormal) behaviour, no (abnormal) experience, is conceivable. Psychiatric disorders are indeed brain disorders. However, they are no less disorders of the soul. The consequences of souls in despair, owing either to external circumstances or to inner turmoil caused by imperfect personality makeup or to both. Ultimately, I mean, in the final analysis, the makeup of a personality, including its flexibility and adaptability, are somehow embedded in brain functioning. However, for all intents and purposes, brain studies have little to offer in understanding the individual soul: how it is structured, how it came to be, how it responded to life’s tribulations, what its hopes and expectations are—at least for the time being and probably for a very long time. The soul is a derivative of the brain and, simultaneously, a territory in its own right. A territory to be studied by soul searchers, soul researchers, and soul healers. It would not be in the interest of psychiatry nor its clientele if the soul regresses into a mere appendage of the brain.

Finally, the points about which I agree with Dr Shorter. The dimensional model will move us from the frying pan into the fire, at least as far as biological psychiatry is concerned. Dimensions are even less precisely definable than psychopathological symptoms are, and even less easy to distinguish from adjacent constructs. This makes them unsuitable as starting points for biological research. Ill-defined, man-made constructs will not easily find their neurobiological counterparts.

I reach the following conclusion. The Kraepelinean diagnostic model was based on the idea that mental pathology is subdividable in discrete disease entities, each with its own pathophysiology. However, this model 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. They cannot be expected to be based on well-defined neurobiological processes

The rigid nosological approach has had its time, particularly in biological psychiatry. It has to retreat in favour of a dynamic–functional disease concept. The largely man-made nosological entity should not be its focus, neither should the syndrome, so often capricious in its symptomatological composition, nor the psychopathological dimension, almost by definition ill-defined and hard to demarcate, but rather the psychic dysfunction underlying the psychopathological symptom. This approach will lead, I assume, to accelerated scientification of psychiatric diagnosis and to a greater yield of biologic psychiatric research.^{1,2}

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