Overview

Psychopathology

Psychopathology 2009;42:1–10
DOI: 10.1159/000173698

Received: July 24, 2007
Accepted after revision: March 20, 2008
Published online: November 20, 2008

A Proposal for a New Multiaxial Model of Psychiatric Diagnosis

A Continuum-Based Patient Model Derived from Evolutionary Developmental Gene-Environment Interaction

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Key Words
Psychiatric diagnosis · Multiaxial model, patient-orientated · Genetics · Diagnostic and Statistical Manual of Mental Disorders · Evolution

Abstract
Background/Aims: To review recent genetic and neuroscientific research on psychiatric syndromes based on the current diagnostic scheme, and develop a better-fitting multiaxial patient-oriented diagnostic model. ***Methods:*** DSM I, published in 1952, considered psychiatric illnesses as reactions or extremes of adaptations of the patient's personality to stressful environmental demands. Personality itself was determined by constitution and psychodynamic development. In 1980, this continuum model gave way to an atheoretical categorical diagnostic scheme (DSM III), based on research diagnostic criteria for obtaining 'pure cultures' of patients for biological research. Subsequent research using the 'pure cultures' suggests that psychiatric syndromes represent a phenotypic continuum determined by genes, childhood traumas, and recent stress, mitigated by childhood nurturance, education, and current social support. Specific gene × childhood abuse × recent stress interactions have been discovered, which may serve as a model of how interacting vulnerability genes may or may not result in a psychiatric syndrome, depending on the individual's developmental history and current stress. ***Results and Conclusion:*** A continuum model is proposed, with genes interacting with early experiences of stress or nurturance resulting in brain states that may evince minor but persistent symptoms (neurosis) or maladaptive patterns of behavior (personality disorder). The addition of recent or current stress may precipitate a major psychiatric syndrome. While a severe genetic predisposition, such as a mutation, may be sufficient to cause a major syndrome, major psychiatric syndromes are best conceptualized as dysregulation of evolutionarily adaptive brain functions, such as anxiety and vigilance. A new multiaxial model of psychiatric diagnosis is proposed based on this model: axis I for phenomenological diagnoses that include major psychiatric syndromes (e.g. depressive syndrome, psychosis), neuroses, personality disorders, and isolated symptoms; axis II for geno-neuroscience diagnoses, some of which may represent biological conditions associated with axis I, i.e. genes, specific brain morphology, and the functional state of specific brain areas based on laboratory and imaging studies; axis III for medical diseases and conditions; axis IV for stress (childhood, recent, and current); axis V for psychosocial assets (intelligence, education, school/work, social support, and global assessment of functioning) over past 5 years and current.

Presented in part at the Annual Meeting of the American Psychiatric Association, San Diego, May 22, 2007.

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Introduction

It is time for psychiatric diagnosis to grow out of the current 'atheoretical' chaos of DSM, and to adopt a developmental model based on evolutionary gene-environment interaction.

The first DSM, published in 1952, was based on Adolf Meyer's psychobiology, a model that prominently posited the interaction between constitution, personality, and environment [1]. Psychiatric disorders were considered to be 'reactions' of the personality while adapting to environmental demands. DSM III dropped the psychodynamic view of etiology and the notion of neurosis, i.e. that there is a continuum between the normal and the psychiatrically ill. It adopted, to a large measure, the 'research criteria for psychiatric diagnosis' that was designed to choose 'pure cultures' of major psychiatric disorders for genetic research [2]. DSM III and its direct successor, DSM IV (1994), classify major psychiatric syndromes into largely mutually exclusive categories (e.g. schizophrenia vs. schizoaffective disorder), presumably based on the notion of different genetic underpinnings. Another prominent feature of DSM III and IV is the multiaxial system of diagnosis.

What Is Right and What Is Wrong with the Current Scheme?

DSM III and IV have helped foster psychiatric research by defining reliable populations for study [3]. They have also pioneered the notion that diagnosis is more than the listing of diseases – it also includes the personality aspect of the patient, as well as the role of stress and the level of functioning. It is an attempt to diagnose the patient, and not merely the disease [4].

There are, however, a number of problems with the current DSM, namely:

Confusion concerning Categories. Any clinician attempting to use DSM III or IV realizes that the diagnostic criteria often seem arbitrary. While it is possible to assign a patient mechanically to one diagnosis or another, it often makes no clinical sense. We often realize that there are patients who almost meet the criteria, or meet most of the criteria for more than 1 category. Examples include the differentiation between schizophrenia and schizoaffective disorder, making the diagnosis of borderline personality disorder, and classifying psychosis in a patient with the history of both schizophrenia and substance use. Genetic research of probands with categorical diagnoses has shown that, in fact, these categories are often heterogeneous, i.e. that many different genes may underlie the same category, such as in schizophrenia and bipolar disorder [5, 6], and that one or a few genes may underlie many different categories, such as bipolar disorder, schizoaffective disorder, and schizophrenia [7–11]. The 'biological underpinnings' have been shown to be for brain states and traits that may be associated with a variety of psychological/functional predispositions [12], and may deserve a status independent of a specific axis I diagnosis.

Confusion concerning the Distinction between Axis I and Axis II. What is the distinction between a personality disorder and a major psychiatric disorder? Where does a borderline personality with a psychotic episode belong in this scheme? Some genetic studies have also shown that there may be a continuum between personality disorder and a major psychiatric syndrome, e.g. borderline personality and bipolar disorder [13, 14].

Confusion concerning the Nature and Function of Multiaxial Diagnosis. What is the multiaxial diagnosis the diagnosis of? Axes I and II are diagnostic categories with explicit criteria, axis III is a diagnosis without explicit criteria, axis IV is a list of stressors, and axis V is a scale. Axis IV and V are, strictly speaking, not diagnoses at all.

What Are the Roots of the Problems with the Current Scheme?

The problems of DSM III and IV are rooted in 2 major areas. One is that they are based on a conceptually faulty notion that psychiatric illnesses are categorical and discrete. The second is that the multiaxial system is a hodgepodge of interesting and important areas to consider in making a diagnosis that lacks conceptual rigor.

While discussing these problems with the current DSM, McHugh [15–18] called for a rethinking of psychiatric diagnosis along the 'perspectives' of disease, dimensions, behavior, and life story. He proposed that mental illnesses be considered in 4, nonmutually exclusive, clusters: (1) disease (e.g. schizophrenia), (2) psychological vulnerabilities (e.g. emotional stability), (3) behavior (e.g. alcoholism), and (4) distress evoked by events (e.g. grief). Some have called for the 'dumping' of DSM altogether, in favor of the disease codes of ICD-10 [19].

The overarching problem of the current DSM is that it lacks a coherent conceptual model of psychiatric illness, which, in the light of modern understanding, is behind

the times. In view of the advantages of DSM discussed above, however, what is called for is a reconceptualization, not the abandonment, of the multiaxial model of diagnosis.

Modern Model of Psychiatric Illness

Since the adoption of DSM III and IV, exciting developments have occurred in molecular biology and genetics. Psychiatric research, at least in part fostered by the rigorous diagnostic criteria of DSM III and IV, has made breathtaking advances, and has taken full advantage of these and other developments, including neuroimaging. This allowed the emergence of a new rational theoretical model of psychiatric illness that is open and evidence based.

Evolutionary Considerations

Many putative genes that code for vulnerability for psychiatric syndromes are evolutionarily conserved and serve adaptive functions. This explains why schizophrenia, which is associated with low fertility rates in the afflicted, has not become extinct.

Certain genes that endow vulnerability to anxiety, e.g. the short allele of the serotonin transporter promoter gene, may confer sensitivity to the 'smoke detector' of anxiety activation [20] and have been evolutionarily adaptive when humans dwelled in caves in fear of predatory animals. In the modern world, however, such sensitivity to anxiety would be dysfunctional for the individual, and thus be considered a psychiatric syndrome.

Gene-Environment Interaction and Brain Morphology/Function

The genes coding for predisposition to various psychiatric syndromes are currently being defined. As far as psychiatric diagnosis goes, the current state of affairs can be summarized as follows: for each diagnostic category, there are many susceptibility genes, and a single gene or a few genes may code for the susceptibility for many different disorders. On the basis of genetic studies, Kendler et al. [21] proposed that psychosis be reclassified as: (1) classic schizophrenia, (2) major depression, (3) schizophreniform disorder, (4) bipolar-schizomania, (5) schizodepression, and (6) hebephrenia.

What seems clear is that the current axis I disorders are syndromes, i.e. the phenomenological convergence of a number of different genetic-pathophysiologic pathways. An analogy might be hypertension. Hypertension is a syndrome that has definable signs and complications that can be treated with 'anti-hypertensive' drugs. Hypertension, however, is etiologically heterogeneous – e.g. it may be nephrogenic, cardiogenic, neurogenic, endocrine, secondary to familial hyperlipidemia or stress-induced.

Gene-Environment Interaction Affects Personality Traits, Brain Morphology, and Risk of Major Psychiatric Illness

An example of a single gene that codes for the vulnerability to multiple psychiatric (and medical) conditions is the serotonin transporter gene *(SERT)* and its promoter region polymorphism (5-HTTLPR). *SERT* is highly evolutionarily conserved, and regulates the entire serotoninergic system and its receptors. DNA screenings of patients with autism, attention-deficit hyperactivity disorder, bipolar disorder, and Tourette's syndrome have detected signals in the chromosome 17q region where *SERT* is located [8]. The 5-HTTLPR polymorphism consists of short (s) and long (l) alleles, and the presence of the short allele tends to reduce the effectiveness and efficiency of *SERT*. The short allele has also been identified as predisposing carriers to anxiety, increased neuroticism scales, smoking (especially to reduce negative mood and feel stimulated), difficulty in quitting smoking, social phobia, major depression, and irritable bowel syndrome [22–25].

Why does a single gene code for so many traits and vulnerabilities? One simple answer may be that the gene codes for one or more basic evolutionarily adaptive predispositions that, in combination with other factors, may determine the development and severity of a psychiatric syndrome. When we look at the list of vulnerabilities above, it seems clear that there is a continuum, from anxiety to adaptive/maladaptive behavior to phobia to major depression, and/or to physical symptoms. The concept of endophenotype is useful in understanding traits associated with syndromes (e.g. eye-tracking abnormality in schizophrenics and relatives) [26], and might provide clues for a genotypic diagnosis.

Pezawas et al. [27] showed that the short-allele carriers show reduced gray matter in limbic regions critical for the processing of negative emotions, particularly the perigenual cingulate and amygdala. They also show increased amygdala activation to fearful stimuli [28, 29]. Thus, this gene seems to increase the sensitivity of the affected individual's brain to negative affect and anxiety [30]. What other factors, then, may further predispose the individual to a major depression episode?

Caspi et al. [9, 10] have shown, in an elegant longitudinal study, that stress during the previous 2 years in adulthood and maltreatment in childhood interacted with the 5-HTTLPR status. Individuals with 2 copies of the short allele who also had the stressors had greatest amount of depressive symptoms and suicidality than heterozygous individuals [9, 10, 31–36], and those with only the long alleles had the least amount of depression. The short allele carriers have been shown to have more neuroticism scores on the Eysenck Personality Inventory, and those with both short allele and high neuroticism were at a higher risk of developing lifetime depression [37].

Studies in monkeys have shown that the anxiety-enhancing effect of the short allele is mitigated with good mothering in infancy [38–40].

5-HTTLPR may also determine the response to drugs. Depressed individuals with the short allele were found to respond better to antidepressants that are both serotonergic and noradrenergic (i.e. mirtazapine), rather than serotonin specific reuptake blockers. On the other hand, individuals with the long allele may have more side effects with exactly those drugs that are more effective for those with the short allele [41]. A dietary deficiency in the serotonin precursor, tryptophan, has been shown to induce depression in healthy women with the 5-HTTLPR s/s, regardless of their family history of depression, while those with l/l were resistant to depression regardless of family history of depression [42–46].

Thus, the 5-HTTLPR short allele, in conjunction with childhood stress, may confer an individual with a trait of responding to later stress with increased anxiety, neuroticism, and subclinical depression [47], which, in turn, may predispose the individual for later major depression, suicidality, bulimia [48] and psychophysiologic disorders. Other gene-environment interactions predisposing individuals to traits and disorders have been reported, including the type 4 dopamine receptor gene *(D4DR)* to novelty seeking and ADHD [49, 50], monoamine oxidase A *(MAOA)* to antisocial personality [9, 51] and dopamine transporter gene *(DAT1)* to ADHD [52].

Emerging Model of Illness

It seems clear, then, that the modern model of psychiatric and medical illness must be based on gene × environment interaction. This model posits that the 'vulnerability gene' has an evolutionarily adaptive function, as evidenced by its very conservation. It holds that there are critical interactions between the genotype and early environment in forming a personality trait, which may in turn be adaptive or maladaptive at the individual level, e.g. anxiety prone, exploratory, attention fluctuating, hypervigilant, etc. Kandel [53, 54] showed how the environment (and learning) modifies gene expression. Our model posits that recent or current stress may play the role of tipping the balance from a trait to a syndrome that has a course of its own. This is a model that is implicit in the works of many investigators, and has been proposed by many others including Caspi et al. [9, 10], Kendler et al. [55], Pezawas et al. [27], as well as McHugh and Slavney [18]. What I am proposing is that this model should now be applied to psychiatric diagnosis. I suggest that there are 4 implications of the emerging model of psychiatric diagnosis: (1) psychiatric diagnosis must include 2 components – the phenomenological and neurobiological. The phenomenological diagnosis should not be categorical but dimensional (axis I); (2) there should be a separate and independent axis for the neurobiological diagnosis that reflects the status of genes and brain morphology/function, which may, but does not necessarily, underlie or predispose towards the phenomenological diagnosis (it could even be asymptomatic); (3) early and recent, as well as current, stressors that might interact with the above diagnoses must be recognized (axis IV), and (4) the importance of psychosocial assets and supports that may modify the stresses (axis V) must be recognized. Such recognition will receive only lip service unless it is codified in a diagnostic scheme, and this we should do by reconceptualizing the axes as outlined above. This codification will provide a schema that will facilitate research in each of the axes and their interactions.

Diagnosing the Patient

Diagnosis derives from the Greek 'dia', meaning through or across, and 'gnosis', meaning knowing. 'Knowing through' or 'knowing across' what? Diagnosis must be the knowledge of the whole of the patient. DSM III and IV were attempts toward this goal, though the goal was not explicitly stated, and thus suffered conceptual confusion.

Medical diagnosis in the last century underwent a major transformation, i.e. from syndromic (illness) to etiologic (disease), largely due to advances in genetics and biochemistry. This spectacularly successful reductionistic approach, however, was often not accompanied by comparable attention to the patient as a whole. Should psychiatry follow the footsteps of medicine? The multiaxial diagnosis in psychiatry potentially allows us to

avoid the pitfalls of replacing illness with disease. For psychiatry, at least, both illness (the experiential, suffering dimension) and disease have to be recognized and treated. Currently, however, all axis I and II diagnoses are syndromes, and, as we have noted, each syndrome probably has a number of different genetic/neuroscientific underpinnings, each of which, in turn, gives rise to different combinations of syndromes depending on the developmental history. For example, the 5-HTTLPR s/s may underlie depressive syndrome, anxiety syndrome, risk-aversive personality, and irritable bowel syndrome. Should 5-HTTLPR s/s replace all of the syndromes as an etiologic diagnosis, at the expense of knowing what the patient's suffering is?

We need a separate axis for the psychiatric illness – the phenomenological, experiential dimension of the patient, such as depression, anxiety, and psychosis – and a separate axis for the genetic/neuroscience disease/vulnerability diagnosis. The differential diagnosis of the syndrome, e.g. depression, would not be major depression versus bipolar disorder versus schizoaffective disorder versus mood disorder secondary to general medical condition versus substance induced mood disorder, etc. The differential diagnosis would instead be: what are the contributions to the depressive syndrome by the specific brain dysfunction, specific genes, and early experiences? Could substances also have contributed to the depressive syndrome? What recent stresses also contribute, are there psychosocial support systems that may be mitigating the extent of the depressive syndrome?

When the existence of a genetic/neuroscientific disturbance is apparent, then a differential diagnosis of this condition should occur following the medical model. This approach will firmly establish the notion that both the illness and the disease require attention and care. This approach would also apply to general medicine.

Psychiatric Diagnosis: Dysregulation and Final Common Pathway Syndromes, and the Resurrection of Neurosis

With the advent of DSM III and IV, it was hoped that psychiatric disorders, as with medical illnesses, would give way to discrete etiologic diagnoses underlying them, perhaps, schizophrenia type I that would turn out to be associated with a discrete gene mutation. Research has shown, however, that there are numerous 'vulnerability' genes that subserve normal functions, but may also, in some instances, cause certain aspects of a syndrome (e.g. psychosis in mood disorders, depression in anxious patients).

Our new model is a continuum model, with genetic endowment for adaptive functions that may become dysfunctional. Of course, there are exceptions, such as a detrimental mutation. There is also the possibility of 'cliff edge phenomenon', where an increased expression of an evolutionarily adaptive genetic trait may reach a point of sudden maladaptiveness, perhaps as in the case of vigilance [56].

Most psychiatric conditions are syndromes of dysregulation. Anxiety is normal and necessary, but when it becomes panic, and is repeated without provocation, it is dysregulated anxiety and needs treatment. So are sadness and depression, vigilance and paranoia, creativity, 'out of the box thinking' and psychosis, brave exploration and antisociality. We should also recognize personality traits and symptoms that border between normality and serious autonomous psychiatric syndromes. I suggest resurrecting the term 'neurosis' to designate these mild to moderate psychiatric conditions. Neurosis serves as an intermediate diagnosis between normality and major final common pathway syndromes, and would encompass various traits and symptoms that represent gene-environment interaction (interaction includes simple additive effect as well as synergy and mitigation) and early learned behaviors.

This continuum model does not mean that we should not have a line of distinction between neurosis and major psychiatric syndromes. Major psychiatric syndromes, such as depressive syndrome and psychosis, however, should be a designation of the expectable autonomous course of the illness, rather than mutually exclusive categories. Such major psychiatric syndromes are final common pathway syndromes that reflect a common brain functional pathology (e.g. hyperactive D_2 receptors in the mesolimbic system) with heterogeneous genetic and biochemical contributions (e.g. drug-induced psychosis). One patient may have multiple psychiatric syndromes as well as neuroses.

The evidence that psychotherapy affects the brain function/structure [53, 54, 57–59] further supports the necessity of reintroducing the notion of neurosis, as the psychotherapy thereof might actually prevent the full development of a major syndrome, as would other preventive measures (such as social support and the protection of children from violence and abuse).

There is overwhelming evidence that social support mitigates stress and the precipitation, maintenance, and prognosis of symptoms of major psychiatric disorders [60–63].

The new system, therefore, must have 3 new entities reflected in the axes: (1) the genomic/brain morphological/functional dimension, which we will call the geno-neuroscience diagnosis; (2) early, recent, and current stress; (3) the protective psychosocial assets of the patient.

Proposal for a New DSM Scheme

I propose that the axes of the new DSM consist of the following:

Axis I: phenomenological diagnosis – psychiatric syndromes, traits, and symptoms.

Axis II: geno-neuroscience diagnosis – relevant genes and brain states.

Axis III: medical diseases and conditions.

Axis IV: stresses – childhood, recent past, and current.

Axis V: psychosocial assets – protecting and/or mitigating against disease and functional state, past 5 years and current.

Relationship among the axes: each axis is conceptualized as aspects of the patient that require understanding and that influence each other, and provide a snapshot of the major factors that must be considered in the management of axis I, II and III.

Axis I: Psychiatric Syndromes, Symptoms, and Traits

This axis will represent the phenomenological psychiatric illness of the patient. This approach accepts the suffering dimension of the patient on its own level, no matter what the underlying etiology is. Operationally, axis I diagnoses are non-mutually exclusive major syndromes and neuroses defined by prominent symptom complexes and would include: psychosis (acute, chronic, type I, type II), depressive syndrome, bipolar syndrome, neurosis (anxiety, depressive, borderline, etc.), posttraumatic stress syndrome, behavioral disorders (substance dependence, antisocial, etc.), cognitive syndromes (delirium, dementia, etc.), psychological factors affecting physical condition, situational reactions, and isolated psychiatric symptoms, e.g. anxiety, depressive affect associated with bereavement, etc.

Currently, axis I diagnoses provide little guidance in psychopharmacology as current drugs often lack specificity for the particular axis I disorder. Defining axis I explicitly as phenomenological diagnoses clarifies the fact that current psychopharmacologic agents are symptom targeted.

A patient could be diagnosed with obsessive-compulsive personality traits, obsessive-compulsive neurosis, depressive neurosis, and depressive syndrome. The diagnosis would not use rigid criteria, but list 1 or more characteristic features. This scheme is compatible with current medical diagnostic practice where hypertension, hyperlipidemia, edema, nephrotic syndrome, diabetic nephropathy, and type II diabetes mellitus might be diagnosed in the same patient.

Axis II: Geno-Neuroscience Diagnosis

I conceptualize this axis to consist of relevant genes and brain states that may explain or contribute to an understanding of phenomena in any axis, mainly through traits and dispositions that interact with the environment and may result in vulnerabilities or predictors of the drug response. We may be initially content with a listing of available genomic and neuroimaging findings, e.g. 5-HTTLPR s/l, subgenual cingulate hyperactivity, hippocampal atrophy, etc.

I expect that this category will be a work in progress for a while, as potential diagnoses in this axis have so far been thought of as mere biological underpinnings of axis I. In fact, it may explain axes III and V rather than axis I, as in a patient with irritable bowel syndrome and the 5-HTTLPR s/s genotype whose anxiety is only moderate. Axis II diagnoses are more likely to be the biological underpinnings of psychological and physical dispositions equally relevant to medicine and psychiatry. By establishing axis II as an independent dimension for the geno-neurobiological state, we can eschew the unnecessary argument as to whether the psychiatric syndrome in axis I is 'biological' or 'psychological' in origin. It also obviates the futile quest for finding the biological underpinnings of arbitrarily defined axis I disorders [64].

Eventually, we may be able to make a genomic-etiologic-pathophysiologic diagnosis, e.g., 5-HTTLPR s/s with amygdala hypertrophy, etc. The entities in axis II would eventually illuminate, together with axis IV, how axes I, III, and V may have evolved – as well as suggesting potential interventions specifically designed for this neurocircuit dysfunction that may be both pharmacologic and psychotherapeutic. Until such refinement occurs, any identifiable putative biological factors should be listed here, including gene variations as in 5-HTTLPR, *MAOA*, and *DAT1*. It should also include abnormalities in brain imaging studies including MRI, fMRI, SPECT, PET, and CT.

Some genomic findings now may have a bearing on the choice of psychopharmacologic agents [65–70].

These conceptualizations of axes I and II will promote research as tests for associations and correlations among items between the axes are likely to reveal new ways in which psychiatric syndromes, personality traits, etc. are associated with specific genes and specific areas and functions of the brain.

Axis III: Medical Diseases and Conditions

Axis III would maintain the current scheme of listing medical conditions and diseases.

Axis IV: Stresses – Childhood, Recent, and Current

Entries in this axis are the factors that potentially contributed to the personality trait and neuroses, and may have set the stage for the major psychiatric syndrome in axis I.

Axis V: Psychosocial Assets and Recent/Current Functioning

A thorough knowing of the patient is not possible without considering the assets as well as liabilities of the patient. This axis should provide information about the protective and mitigating factors for health rather than illness. They would include intelligence, educational level, school and work history, and social support. I would propose maintaining the global assessment of functioning (GAF) of the current DSM at the end of axis V, but extend the GAF from the past year to the past 5 years to account for functioning before recent stresses in axis IV, and to express it in a single fractional number: previous 5 years GAF/current GAF, expressed as 70/40.

What is a Diagnosis for?

Diagnosis serves 2 purposes: an intellectual understanding of the condition at hand, and, more importantly, it should lead to logical treatment strategies. With our patient model of diagnosis, the interaction of the 5 axes should lead to an interactional diagnostic formulation such as: depressive syndrome (axis I), subgenual cingulate-amygdala circuit dysfunction (axis II) associated with 5-HTTLPR s/s (axis II), contributed by childhood abuse and recent divorce (axis IV), resulting in a temporary decline in function (axis V 80/40), in a person with a high educational level and intelligence (axis V) and supportive friends (axis V). Diagnosing each of the components can directly suggest treatment approaches that can be prioritized by the clinician. For example, psychotherapy may be indicated for the axis IV diagnoses, not only to deal with the stress of divorce but also potentially to reverse the gene alterations caused by childhood abuse [9, 10], and to reverse the subgenual cingulate-amygdala circuit dysfunction. The diagnosis of 5-HTTLPR s/s may also suggest that the clinician should prescribe mirtazapine rather than selective serotonin reuptake inhibitors, as well as alerting the clinician about possible comorbidity with irritable bowel syndrome and a propensity for anxiety symptoms.

It is time to stop tinkering with the existing scheme, and to boldly reconceptualize the multiaxial diagnosis of the patient.

Discussion and Limitations

This model is strongly based on evolutionary and biopsychosocial perspectives, and does not explicitly incorporate other important perspectives in diagnostic nosology [71–73]. By adopting a rigorous evolutionary and gene-environment interaction model, I believe this model avoids the 'intellectual laziness' attributed to the biopsychosocial model [18, 71]. While the use of the evolutionary gene-environment interaction to determine neurotic tendencies and major psychiatric syndromes is applicable to most psychiatric conditions, including anxiety, depression, mania, and psychosis, there may be other psychiatric conditions that do not require such an interaction. The proposed model explicitly does not prescribe axes II or IV to be etiologic of axis I, but rather that they require independent consideration for possible linkage. For example, meta-analysis of the role of *SERT* in major depression and bipolar depression showed only a weak association [22]. *SERT* is now known to have 3 allelic forms: S, L_a and L_G. As L_G behaves like the short (S) allele, older studies using only S and L alleles may have diluted the differences. The weak association may also indicate that *SERT* is not the biological underpinning of the major syndromes, but rather of the disposition to a variety of brain states, some of which may, in interaction with other genes and development, result in the syndromes.

A recent study indicates that *SERT* interacts with catechol-*O*-methyltransferase and life stresses in the development of depression [74]. There are clearly other genes that may play a similar role. The purpose of proposed axis II is to record such identified genes and/or brain states, which may eventually turn out to be useful in intervention (as in the case of genetic hyperlipidemia, which is a small portion of persons at risk for, say, stroke). Some may argue

that the proposed axis II may result in more expensive diagnostic procedures such as functional MRI and genotyping. MRI, now used routinely, was expensive in the beginning, but the benefits now far outweigh the cost. Tests to establish the axis II diagnoses will surely result in more effective and less costly treatments in the long run.

I believe the biopsychosocial aspect of the model is more pluralistic than eclectic [71], and it is practical, operational and likely to stimulate research. For an understanding of neurotic symptoms and problems of living (isolated psychiatric symptoms) on axis I, existential and cultural perspectives, among others, may play an important role [72, 73]. Such factors, however, naturally belong in the life history of the patient and cannot simply be listed in a diagnosis, but they should be important factors to consider in treatment.

Some might consider the patient model to be over inclusive, and that diagnosis should be of the disease in the Oslerian tradition. It is our contention that diagnosis, particularly psychiatric diagnosis, must consider the phenomenological diagnosis (axis I) in parallel with the disease (axis II). An advantage of the DSM III and IV multiaxial diagnoses is that diagnoses exist in different dimensions of the patient, but they did not go far enough and are not logical enough to delineate the axes.

Our model does not explicitly address an important consideration in diagnostics: values [75]. I believe that this model reduces the negative valuation of mental illness through the continuum model. The evolutionary perspective that the genes that potentially contribute to current suffering have adaptive value also mitigate such negative valuation. The proposed multiaxial system that includes consideration of strengths as well as pathology will also lead to more individualized care.

Who should make a multiaxial diagnosis? Qualified mental health professionals could certainly make phenomenological diagnosis on axis I, and appropriate entries on axis IV and V. Qualified physicians could make axis III diagnosis. Psychiatrists and other physicians with specialized training would be qualified to make proposed axis II diagnosis. Psychiatrists would be the most qualified professionals to integrate all the axes in formulating rational treatment for the patient.

Looking Back and Looking Forward

A half-century after the advent of the first DSM, based on Adolf Meyer's psychobiology, we discover anew with deeper understanding that the Meyerian model of interaction between the constitution, development, and personality of the human organism in adapting to environmental demands still holds true. We now know that genes interact with early stress in the shape and function of brain structures, and prolonged stress affects the longevity of cells by shortening their telomeres [76]. With these advances, we are now in a position to truly diagnose the patient's behavior, emotions, and cognition.

What will the future hold for the new diagnostic scheme? I hope that this scheme will foster research that tests associations among the 5 axes, as well as within each axis. It should be possible to tease out the contributions of genes (axis II) and early stress (axis IV) in determining the brain's functional state (axis II), which, in interaction with the individual's psychosocial strengths (axis V) and current stress (axis IV), may result in mild psychiatric symptoms, neurosis, or a major psychiatric syndrome (axis I). I anticipate that axis II will swell and then settle into discrete interrelated combinations of genotypic and phenotypic functional-morphologic clusters (for example, s/s 5-HTTLPR combined with hypotrophy of the subgenual cingulate and amygdalae, which, in turn, may acquire a simpler disease name) that are associated with a number of axis I entities, e.g. depressive neurosis and depressive syndrome, anxiety neurosis and psychosis, etc. Research into the association between axis I and axis II diagnoses should promote the development of pharmacogenomics and more effective and specific drug treatment. Consistent findings that certain axis I diagnoses are not associated with any axis II diagnosis may indicate that these diagnoses, in fact, are predominantly the result of learning maladaptive behaviors. The new multiaxial diagnosis of the patient that includes the individual's strengths as well as vulnerabilities will assist us in the selection of the best treatment approaches for the patient.

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