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Making psychiatric semiology great again: A semiologic, not nosologic challenge

Jean-Arthur Micoulaud-Franchi, C. Quiles, Jean-Marie Batail, C. Lancon, M. Masson, Guillaume Dumas, M. Cermolacce

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1 Making psychiatric semiology great again:
2 a semiologic, not nosologic challenge
3 *Perspective / Opinion*
4

5 Jean-Arthur MICOULAUD-FRANCHI^{1,2*}, Clélia QUILES^{3,4}, Jean-Marie BATAIL^{5,6},
6 Christophe LANCON^{7,8}, Marc MASSON^{9,10}, Guillaume DUMAS^{11,12,13,14}, Michel
7 CERMOLACCE^{7,15}

- 8 1 - Services d'explorations fonctionnelles du système nerveux, Clinique du sommeil, CHU de Bordeaux, Place
9 Amélie Raba-Leon, 33076 Bordeaux, France.
10 2 - USR CNRS 3413 SANPSY, CHU Pellegrin, Université de Bordeaux, France.
11 3 - Centre Hospitalier Charles Perrens, Pôle Universitaire de Psychiatrie Adulte, 121 Rue de la Béchade, 33076
12 Bordeaux Cedex, France
13 4 - Université Bordeaux Segalen, 146 rue Léo-Saignat, 33076 Bordeaux Cedex, France
14 5 - Academic Psychiatry Department, Centre Hospitalier Guillaume Régnier, Rennes, France
15 6 - EA 4712 Behavior and Basal Ganglia, CHU Rennes, Rennes 1 University, France.
16 7 - Pôle de Psychiatrie "Solaris", Centre Hospitalier Universitaire de Sainte-Marguerite, 270 Bd de Sainte-
17 Marguerite, 13009 Marseille, France.
18 8 - Laboratoire de santé publique évaluation des systèmes de soins et santé perçue, Université de la Méditerranée
19 - EA 3279 - Faculté de Médecine, 27 bd Jean Moulin, 13385 Marseille cedex 05, France.
20 9 - Nightingale Hospitals Paris-Clinique du château de Garches, France
21 10 - Service hospitalo-universitaire, Centre Hospitalier Sainte-Anne, 75015 Paris, France
22 11 - Institut Pasteur, Human Genetics and Cognitive Functions Unit, Paris, France
23 12 - CNRS UMR 3571 Genes, Synapses and Cognition, Institut Pasteur, Paris, France
24 13 - University Paris Diderot, Sorbonne Paris Cité, Paris, France
25 14 - Centre de Bioinformatique, Biostatistique et Biologie Intégrative, Paris, France
26 15 - Laboratoire de Neurosciences Cognitives (LNC), UMR CNRS 7291, 31 Aix-Marseille Université, Site St
27 Charles, 3 place Victor Hugo, 13331 Marseille cedex 3, France
28

29 * Corresponding author:

30 Dr. MICOULAUD FRANCHI Jean-Arthur
31 Services d'explorations fonctionnelles du système nerveux, Clinique du sommeil, CHU de
32 Bordeaux, Place Amélie Raba-Leon, 33076 Bordeaux
33 E-mail adresse : jarthur.micoulaud@gmail.com
34

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1 **Abstract**

2
3 This article analyzes whether psychiatric disorders can be considered different from non-
4 psychiatric disorders on a nosologic or semiologic point of view. The supposed difference
5 between psychiatric and non-psychiatric disorders relates to the fact that the individuation of
6 psychiatric disorders seems more complex than for non-psychiatric disorders. This
7 individuation process can be related to nosologic and semiologic considerations. The first part
8 of the article analyzes whether the ways of constructing classifications of psychiatric
9 disorders are different than for non-psychiatric disorders. The ways of establishing the
10 boundaries between the normal and the pathologic, and of classifying the signs and symptoms
11 in different categories of disorder, are analyzed. Rather than highlighting the specificity of
12 psychiatric disorders, nosologic investigation reveals conceptual notions that apply to the
13 entire field of medicine when we seek to establish the boundaries between the normal and the
14 pathologic and between different disorders. Psychiatry is thus very important in medicine
15 because it exemplifies the inherent problem of the construction of cognitive schemes imposed
16 on clinical and scientific medical information to delineate a classification of disorders and
17 increase its comprehensibility and utility. The second part of this article assesses whether the
18 clinical manifestations of psychiatric disorders (semiology) are specific to the point that they
19 are entities that are different from non-psychiatric disorders. The attribution of clinical
20 manifestations in the different classifications (Research Diagnostic Criteria, Diagnostic
21 Statistic Manual, Research Domain Criteria) is analyzed. Then the two principal models on
22 signs and symptoms, i.e. the latent variable model and the causal network model, are
23 assessed. Unlike nosologic investigation, semiologic analysis is able to reveal specific
24 psychiatric features in a patient. The challenge, therefore, is to better define and classify signs
25 and symptoms in psychiatry based on a dual and mutually interactive biological and
26 psychological perspective, and to incorporate semiologic psychiatry into an integrative,
27 multilevel and multisystem brain and cognitive approach.

28
29 **Key Words:**

30 Nosology; Semiology; Research Diagnostic Criteria; Diagnostic Statistic Manual; Research
31 Domain Criteria; Latent variable model; Causal network model

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1 Introduction

2 A passionate long-lasting debate in medicine is knowing “what kinds of things are psychiatric
3 disorders?” [1]. This question has engendered complex historical, sociological,
4 epistemological and philosophical concepts with large differences between models and
5 schools of psychiatric thought [1-7]. Such thinking is essential for the development of
6 psychiatric medicine but commonly gives the implicit impression that psychiatric disorders
7 are something different or quite different from non-psychiatric disorders. This purported
8 distinction is particularly evident in the traditional dichotomy between mental and physical
9 disorders. However, psychiatry, like the entire field of medicine, should go beyond this
10 dichotomy [8, 9].

11 The supposed difference between psychiatric and non-psychiatric disorders also stems from
12 the fact that the individuation of psychiatric disorders seems more complex than for non-
13 psychiatric disorders. This individuation process can be related to nosologic and semiologic
14 considerations. Nosologic considerations concern the scheme of classification imposed on
15 clinical and scientific medical information to delineate disorders, thereby increasing its
16 comprehensibility and utility. Semiologic considerations relate to the clinical evaluation and
17 organization of signs and symptoms in order to undertake clinical reasoning leading to the
18 identification of a psychiatric disorder [10, 11].¹ This article analyzes whether psychiatric
19 disorders can truly be considered as something different when considered from a clinical
20 nosologic or semiologic point of view.

¹ The term semiology is used in this article as a synonym of the term symptomatology, presentation, manifestation or phenomenology of the disorder. In this article, we use the term semiology, in line with the French medical tradition from the early 19th century. In the English tradition, the term semiology has referred since the middle of the 17th century to the science of language. Thus, the English medical tradition is to use “symptomatology”, “clinical presentation, manifestation or phenomenology”. However, it should also be noted that the term phenomenology used in this sense can be considered as a misuse in clinical psychiatry. Indeed, current usage as a set of signs and symptoms of a patient with a psychiatric disorder is different from the original meaning, which concerned comprehending a patient's subjective self-experience (in line with the continental understanding of phenomenological philosophy).

1 **Are psychiatric disorders different when considered from a nosologic point of view?**

2 The long-standing discussion accompanying the construction of contemporary classifications
3 of psychiatric disorders, in particular the Diagnostic and Statistical Manual of Mental
4 Disorders (DSM) [12], demonstrates that unlike in other medical disciplines, it is not easy to
5 classify disorders in psychiatry, thereby reinforcing the impression that psychiatric disorders
6 are something different. Psychiatric disorders might be entities different from non-psychiatric
7 disorders because the ways of establishing the boundaries between the normal and the
8 pathologic, and of classifying the signs and symptoms in different categories of disorder, are
9 not the same. The first part of the article thus analyzes whether the ways of constructing
10 classifications of psychiatric disorders are different than for non-psychiatric disorders.

11
12 *Evolution of nosologic issues from the RDC to the RDoC*

13 The ways of establishing the boundaries between the normal and the pathologic and the
14 classification of the different disorders have to be evaluated for their reliability and their
15 validity [12].

- 16 - Reliability (also called “precision”) refers to reducing disagreement among clinicians
17 about whether some phenomena are to be considered as pathologic or not and about
18 the psychiatric diagnosis.
- 19 - Validity (also called “accuracy”) is “*the degree to which diagnostic criteria reflect the*
20 *comprehensive manifestation of an underlying psychopathological disorder*” [13].

21 The early contemporary classification, and in particular the Research Diagnostic Criteria
22 (RDC), sought to establish diagnostic criteria in order to enhance reliability in psychiatry
23 [14]. The RDC project was developed at the Washington University School of Medicine in St
24 Louis. The criteria of the St Louis group are also known as the “Feighner criteria”, because
25 Feighner was the author of the seminal article summarizing criteria for 15 psychiatric
26 conditions [15]. The development of the RDC project led to the major revisions in DSM-III
27 [16]. It stated: “*Since in DSM-I, DSM-II, and ICD-9 explicit criteria are not provided, the*
28 *clinician is largely on his or her own in defining the content and boundaries of the diagnostic*
29 *categories. In contrast, DSM-III provides specific diagnostic criteria as guides for making*
30 *each diagnosis since such criteria enhance interjudge diagnostic reliability*” [17]. The
31 expectation was that each psychiatric disorder would be validated by its separation from other
32 disorders. However, the validity of the RDC and the subsequent DSM has been largely
33 criticized [18, 19]. Thus, the Research Domain Criteria (RDoC) was the most important
34 contemporary classification to focus on validity. The aim was to create “*new ways of*

1 *classifying mental disorders based on dimensions of observable behavioral and*
2 *neurobiological measures*” [20]. The RDoC, which interestingly used an acronym very close
3 to the RDC project, was developed at the National Institute of Mental Health (NIMH), an
4 agency of the United States Department of Health and Human Services and the largest
5 research organization in the world specializing in mental illness. Thomas Insel, who led the
6 NIMH from 2002 until 2015, largely supported the RDoC project. By proposing a
7 dimensional approach based on brain function, it was thought that the future nosology of
8 psychiatric disorders would be more valid, i.e. closer to underlying physiopathological
9 mechanisms [18].

11 *Boundaries between the normal and the pathologic*

12 In this section we analyze ways of establishing the boundaries between the normal and the
13 pathologic. The construction of contemporary classifications of psychiatric disorders requires
14 operational criteria to reduce disagreement among clinicians regarding whether a
15 phenomenon are pathologic or not (reliability) and to ensure that it is determined by an
16 underlying impaired physiological mechanism (validity). In this paper, we term “inclusion
17 criteria” the defining criteria used to address reliability and to identify signs and symptoms
18 that may be considered as “clinically significant”; and “exclusion criteria” the defining
19 criteria used to address validity and to identify signs and symptoms that are not to be
20 considered as pathologic. How specific criteria are designed to position the boundaries
21 between two disorders will be analyzed in the following section.

22 In the RDC, these additional criteria were not explicitly defined. However, Feighner et al.
23 stated that *“the first step is to describe the clinical picture of the disorder. This may be a*
24 *single striking clinical feature or a combination of clinical features thought to be associated*
25 *with one another. Race, sex, age at onset, precipitating factors, and other items may be used*
26 *to define the clinical picture more precisely. The clinical picture thus does not include only*
27 *symptoms”* [15]. Thus, they clearly indicated that the boundary between the normal and the
28 pathologic should to be determined by features other than only the signs and symptoms. In
29 1978, Spitzer and Endicott proposed a detailed list of operational criteria [21] that are shown
30 in **Table 1**. They are the most detailed operational criteria known for fixing the boundaries
31 between the normal and the pathologic. These criteria were the bases of the reduced criteria
32 published in the subsequent DSM. The criteria of the different editions of the DSM are shown
33 in **Table 2**.

1 The “inclusion criteria” to identify signs and symptoms as “clinically significant” are criteria
2 based on the consequence of the disorder: disability. The DSM-5 specifically discussed the
3 consequence of such a position in the field of medical nosology (p 21.) [13]. Indeed, the
4 classifications developed by the World Health Organization (WHO) have clearly
5 differentiated the concepts of disorder (with the International Classification of Diseases -
6 ICD) and disability (with the International Classification of Functioning, Disability and
7 Health - ICF). Disability refers to the consequence of the disorder and not to its definition. In
8 psychiatric classification, disability is part of the boundary of the disorder. This is an
9 important difference between psychiatric and non-psychiatric disorders, and it is widely held
10 that the boundary of a disorder in medicine is based on a biomarker that reflects its
11 pathophysiological mechanism. However, this is to forget, as Claude Bernard pointed out,
12 that boundaries between the normal and the pathologic cannot be defined primarily on the
13 basis of physiology [9]. A boundary is to be set first on clinical and epidemiological factors
14 pertaining to disability or future disability if no therapy is begun [22]. Biomarkers are the
15 second step and are taken to reflect a disease process explaining the disability or the evolution
16 toward disability. The Spitzer and Endicott 1978 criteria already highlighted this point by
17 using “*a condition in the fully developed or extreme form*” because “*in medicine many*
18 *conditions are recognizable in an early form, frequently with the aid of laboratory tests,*
19 *before they have any undesirable consequences*” [21].

20 Interestingly, these two steps are considered in reverse order by many physicians, who
21 consider that the boundaries between the normal and the pathologic are defined primarily
22 from the point of view of the pathophysiology and biomarker. They do not consider disability
23 as being entirely part of the definition of the disorder. The difference between a psychiatric
24 and non-psychiatric disorder is that the consideration of disability remains directly and
25 explicitly within the realm of psychiatry, whereas this notion may be forgotten because
26 biomarkers exist for non-psychiatric disorders. “*Unfortunately, in psychiatry we rarely have*
27 *laboratory procedures which permit us to diagnose mental disorders before they have clinical*
28 *manifestations*” [21]. Fundamentally, however, the process of differentiating the normal and
29 the pathologic remains the same for psychiatric and non-psychiatric disorders.

30 Nevertheless, in line with Claude Bernard who stressed that the physiological mechanisms
31 underlying a pathology should be described in order for medicine to be considered as
32 scientific, a challenge in psychiatry is to identify biomarkers in order to better evaluate
33 disability and future disability, a process also called clinical staging. “*To test the concept,*
34 *there is a clear need to develop illness markers that (...) have the capacity to track the extent*

1 *of the disease process*” [23]. Biomarkers will also be useful for probing the efficiency of
2 treatments [24] and identifying resilient subjects who could have a biomarker related to a
3 disorder but which does not appear to be affected by the disorder [25].

4 As biomarkers have not been developed in psychiatry, exclusion criteria have been
5 determined to identify signs and symptoms that are not considered to be due to an underlying
6 physiological deterioration, and thus which are not considered to be pathologic. **Table 2.**
7 Indeed, *“the locus of the disturbance in a medical disorder is at least partly within the*
8 *organism”* [21]. *“This does not mean that factors outside of the organism are of no*
9 *importance”* but that *“largely within the organism with regard to either initiating or*
10 *maintaining the condition”* [21]. The DSM criteria seem to be rather imprecise and not very
11 operational, because they are based on general sociological considerations about the
12 relationship between the individual and society. On the other hand, the Spitzer and Endicott
13 criteria determined three criteria to establish whether signs and symptoms can be attributed to
14 a supposed mechanism within the organism (criteria B1, B2 and C, in **Table 1**).

15 The use of such criteria is an important difference between psychiatric and non-psychiatric
16 disorders. In fact, the absence of a biomarker should not mask the fact that the identification
17 of a physiological impairment underlying a disorder is an ideal in medicine that is not
18 absolutely necessary. This ideal was called “the hard medical model” by Kendler, who stated
19 that *“the hard medical model, while historically critical in the evolution of disease*
20 *conceptualization, is in fact an idealization which fully applies to only a small group of*
21 *Mendelian, nutritional, infectious and parasitic disorders”* [26]. Moreover, following on from
22 Spitzer and Endicott who stressed that *“the nature of what is wrong may be known or*
23 *unknown, and may or may not be conceptualized in somatic or physiological terms”*, the
24 MESH defined disease as *“a definite pathologic process with a characteristic set of signs and*
25 *symptoms”* and added that *“its etiology, pathology, and prognosis may be known or*
26 *unknown”*. The very important point here is that the pathophysiological mechanism may be
27 unknown so it is important to conduct scientific research to identify these mechanisms, not
28 necessarily to have them for conducting clinical medicine [27]. Indeed, medicine is also based
29 on clinical science [28, 29]. Nevertheless, the wide field of scientific psychiatric research
30 concerning the investigation of what is wrong inside the brain, and more generally the
31 organism, of patients with a psychiatric disorder places psychiatry entirely and rightfully
32 within the realm of scientific medicine.

1
2 *Classification of different disorders: boundaries between disorders*

3 In this section we analyze how different disorders are classified. The construction of
4 contemporary classifications of psychiatric disorders has led to operational criteria to reduce
5 disagreement among clinicians about psychiatric diagnosis (reliability) and to ensure that the
6 phenomenon is determined by an underlying impaired physiological mechanism (validity).
7 Reliability has been addressed by defining an appropriate list of criteria to identify signs and
8 symptoms that are easily recognized by a clinician and are clustered together. Validity has
9 been addressed by defining criteria that ensure the possibility of different underlying impaired
10 physiological mechanisms for different disorders. These validity criteria were primarily
11 identified by Robin and Gruze in 1970 [30], then added to by Spitzer and Endicott in 1978
12 [21], by Kendler in 1990 [31] and by the DSM-5 in 2013 [13]. **Table 3.**

13 In psychiatric classification, as biomarkers do not exist, a list of validating criteria has been
14 established. This is an important difference between psychiatric and non-psychiatric disorder
15 classifications. Indeed, it is widely considered that the classifications of disorders in medicine
16 are based on biomarkers that reflect pathophysiological mechanisms. However, classifying
17 disorders is a very complex process involving epidemiological, semiologic, prognostic,
18 therapeutic, economic, and genetic factors [27, 32, 33]. **Figure 1.** As posited by Spitzer and
19 Endicott in 1978, *“the operation by which syndromes and disease are distinguished from each
20 other and from symptoms consist of examining the extent to which the external correlated of
21 interest differ. The more they differ, the more likely it is that the condition represents
22 syndrome or disease and not mere symptoms”* [21]. This classification of disorders is in line
23 with the coherence theory of truth that postulates that *“the best diagnoses we have are the
24 ones that are heavily intertwined with other things we know about; that is, are ‘well
25 validated’. For individuals assigned to that class, we follow the strings and see all the other
26 things that we learn about them”* [34]. This paradigm involves the *“examination of the entire
27 medical classification system reveals that no single principle accounts for the allocation of
28 disorders to various subgroupings”* [21]. Of course, all these relations of validation should be
29 integrated in a unified pathophysiological process in which a biomarker is solely the
30 reflection, but not the primarily cause, of the classification. Moreover, in many cases, such
31 biomarkers are in fact a concept resulting from many causes and mechanisms, i.e. *“a
32 therapeutic target rather than an etiological node; that is, not something to find that would
33 explain everything, but something to act upon that would dissolve everything”* [35].

1 The difference between psychiatric and non-psychiatric disorders is that the validators are by
2 and large explicit in psychiatric classifications and we do not have any reliable simple
3 validator for psychiatric diagnoses, whereas they may be forgotten or considered as
4 biomarkers in non-psychiatric disorders. Fundamentally, however, the process of classifying
5 any type of disorder is the same and has to take into account the multifactorial and
6 etiologically complex nature of the explanatory models in medicine [33]. Biological
7 reductionism is less fruitful than explanatory pluralism in most psychiatric and non-
8 psychiatric disorders [32]. One may consider that the DSM-5 implicitly takes explanatory
9 pluralism into account by stating that... *“the boundaries between many disorder "categories"
10 are more fluid over the life course than DSM-IV recognized, and many symptoms assigned to
11 a single disorder may occur, at varying levels of severity, in many other disorders. These
12 findings mean that DSM, like other medical disease classifications, should accommodate
13 ways to introduce dimensional approaches to mental disorders, including dimensions that cut
14 across current categories”* [13]. The question raised by the DSM-5, in line with the RDoC
15 project is whether the actual classification based on categories is the best way to describe the
16 multifactorial and etiologically complex pathophysiological mechanisms implicated in
17 psychiatric disorders. The DSM-5 position underlines the “real paradigm shift” that was
18 proposed by the RDoC project. The RDoC paradigm shifts the heuristic from coherence at the
19 theoretical level to support for experimental observation at the physiological level [36], in line
20 with the traditional translational research approach [37]. Indeed, *“the RDoC does not take as
21 starting point the traditional view of disorders as symptoms complexes based largely on
22 clinical descriptions”* for which validators are required [20]. In contrast, the RDoC considered
23 validity from the point of view of physiological and not clinical dysfunction. Thus, it did not
24 categorize clinical signs and symptoms but proposed a dimensional framework in which the
25 different functions of the brain are considered, and supposed that any of these dimensions can
26 be impaired. However, this dimensional approach raises an important question regarding the
27 link between the physiological and medical approach to a disorder, an issue related to the
28 notion of continuity. Indeed, where do we situate the threshold for considering a brain
29 function as pathologic when we also consider each dimension as being continuous? As
30 discussed previously and summarized by Stein in a comment on the RDoC: *“we need to
31 accept that diagnosis system cannot “carve nature at her joints”. Rather facts and value need
32 to be continually re-assessed, to try optimize classification”* [33].
33 This section has therefore analyzed whether psychiatric disorders differ from non-psychiatric
34 disorders at the nosologic level. We have shown that the lack of biomarkers in psychiatry has

1 led the psychiatric community to clearly and thoughtfully explore the inherent process of
2 establishing the boundaries between the normal and the pathologic and between the different
3 disorders in medicine. This process is as complex in psychiatry as in any other medical field.
4 This does not mean, however, that epistemology of psychiatry ought to be general as part of
5 epistemology in medicine, without the need for regional epistemology [4, 38]. The historical
6 and sociological specificity of psychiatry should not be underestimated. Nevertheless, we
7 believe that the need for a regional epistemology is more semiologic than nosologic. Thus, the
8 question to be asked now is whether psychiatric disorders differ from non-psychiatric
9 disorders at the semiologic level, i.e. with regard to their clinical manifestations.

1 **Are psychiatric disorders different when considered from a semiologic point of view?**

2 The discussions concerning the drafting of the DSM-III surprisingly involved little discussion
3 on semiologic issues in psychiatry. Nevertheless, as stated in the DSM-III, the separation
4 between “physical” (non-psychiatric) and “mental” (psychiatric) disorders is not based on
5 pathophysiological mechanisms (organic versus psychologic) but “*on the tradition of*
6 *separating those disorders whose manifestations are primarily behavioral or psychological*
7 *(i.e., mental disorders) from those whose manifestations are not.*” Identifying psychiatric
8 manifestations was thus a central issue for the authors of the DSM-III in identifying what kind
9 of entity psychiatric disorders really are. **Mental manifestations (symptoms and signs) are**
10 **considered as the “unit of analysis” that has to be captured in order to make a psychiatric**
11 **diagnosis [38].** However, thinking about what a sign or symptom in psychiatry is has not kept
12 in step with reflection on the nosologic aspects of psychiatry [38, 39]. Thus, the second part
13 of this article analyzes whether certain manifestations of psychiatric disorders make them
14 stand apart from non-psychiatric disorders.

15
16 *Evolution of semiologic thinking from the RDC to the RDoC*

17 Symptoms refer to the subject’s that they experience and notice, while signs refer to
18 manifestations that they may experience but which are also externally observable by others
19 [38]. Whatever the type of psychiatric interview [39], the first essential step when identifying
20 psychiatric symptoms and signs is to conduct a clinical reasoning process about the
21 psychiatric disorder and to take the necessary clinical decisions [40]. In line with this medical
22 position, DSM-III discussions focused on operationalizing the criteria in order to enhance the
23 reliability of assessing psychiatric disorders and thus of the diagnosis [41]. The aim was not
24 to reduce clinical psychiatry to a list of criteria but to consider that: “*if the medical*
25 *practitioner confines himself to diagnosis and to treatment based specifically on [diagnostic*
26 *tools], the help he can give (...) is in general severely restricted. (...) However, if the doctor*
27 *cannot make a useful diagnosis, he severely restricts his competence in a different way and*
28 *becomes immeasurably less useful to his patient*” [40]. The RDC was developed with this in
29 mind, the first step in scientific medicine being the clinical examination of patients. In the
30 non-psychiatric fields of medicine, the pride of place accorded to non-clinical results obtained
31 from laboratory tests, imaging, etc. can lead the clinician to ignore the importance of the
32 clinical examination in the development of medicine. However, “to neglect this stage would
33 be to misunderstand the nature of scientific enquiry” [40]. “*Our present sophisticated medical*
34 *knowledge has accrued because of centuries of observation and description, in which the*

1 *describers and classifiers have played as dynamic and creative part as those concerned with*
2 *process” [40]. “No disease theory can be elaborated before the clinical syndrome has been*
3 *recognized and labeled”, “the value of those first step should not be underestimated” and*
4 *“the second step can then be taken, which is to test the validity of various explanatory*
5 *theories”.* **Figure 2.** The RDC project and the resulting DSM criteria were developed in order
6 to enhance the value of the first step. Unfortunately, the list of criteria in the DSM became the
7 reference for semiologic terms in psychiatry, thereby reducing and simplifying the corpus of
8 signs and symptoms [42, 43]. Moreover, the organization of the corpus of signs and
9 symptoms was based on nosologic categories and not on supposed underlying
10 pathophysiological mechanisms. *“In many cases, there are also observable bodily*
11 *abnormalities [physiological abnormalities]; most evident in the case of anxiety states (...),*
12 *but nowhere sufficient in themselves for a reliable classification” [40].* As a result, it was
13 posited that among the many possible techniques for classifying psychiatric symptoms and
14 signs, the easiest to implement was the clinical diagnosis [40].

15 This subordination of semiology to nosology may be of value given the historical aspects of
16 signs and symptoms in psychiatry. Wakefield has called this the “conceptual validity” of
17 signs and symptoms. Conceptual validity has allowed the psychiatric community to
18 *“delineate the domain of psychological condition that fall under the concept of disorder”*
19 [44]. **Indeed,** present-day semiology bears close links to nosographic thinking, which itself
20 can be traced back to historical and “psychosocial” views of the individual. **In other words:**
21 *“Since doctors have been making examinations of ‘mental state’ from time immemorial, they*
22 *do not have to start afresh each time but can utilize the experience of their predecessors”*
23 [40]. **Thus,** rather than semiologic analysis being used as the first step when testing disease
24 theory, it has come to occupy a subservient role to the categorization of psychiatric disorders.
25 **Figure 2.** This role of subservience also means that the relationship between semiology and
26 nosography tends to be inverted. In medicine, it is traditionally postulated that signs and
27 symptoms influence which disorder category is to be employed, but not that the disorder
28 category will influence the types of symptoms and signs that are sought in a patient. In
29 psychiatry, symptoms and signs tend to be influenced by the disorder category [45]. This also
30 means that symptoms and signs in psychiatry tend to contain de facto the boundaries between
31 the normal and the pathologic, and the classification of disorder. In some way, the two-step
32 process in which medicine has developed, i.e. clinical description then neurophysiological
33 theory of disorder, is biased on in that clinical descriptions are largely influenced by concepts
34 of disorder category [46]. As Berrios stated *“the DSM-III two-stage model, according to*

1 *which symptom and disease recognition are independent cognitive events, did not work. (...)*

2 *The disease hypothesis absolutely controls the way mental symptoms are captured and*
3 *recognized” [47]. **Figure 2.***

4 One can even consider that the RDoC project turned the initial project of establishing a
5 classification of psychiatric symptoms upside down [40]. It posited that the first step is not to
6 establish clinical descriptions but to gain neurophysiological knowledge about cognitive and
7 brain mechanisms [18]. By doing so, it is propounds the opposite of what Wing, Cooper and
8 Sartorius say [40]. **Figure 2.** Thus, by turning the two-step process around, the RDoC may be
9 seen as an attempt to reorganize the classification of psychiatric symptoms and signs on the
10 basis of the underlying physiological mechanisms and not on the basis of the historical
11 classification of disorders. Aragona clearly highlighted the fact that the RDoC turns the
12 original project upside down [12]. *“Both the neo-Kraepelinian DSM-III and the DSM-5 are*
13 *based on the same assumption about validity: i.e., the provisional phenomenal descriptions*
14 *(the individual mental disorders or, as in the DSM-5, the larger grouping of adjacent*
15 *disorders) will be fully validated when some specific neurobiological factors are "discovered"*
16 *that confirm that the phenomenal description really corresponds to a neurobiological disease.*
17 *(...) The RDoC project, which is considered the most promising etiopathogenic approach at*
18 *play in current debates, shares with the other etiopathogenic approaches a revolutionary*
19 *shift. While in the neo-Kraepelinian approach validation research is expected to proceed*
20 *from phenomenally defined disorders back to the discovery of their etiology, in the*
21 *etiopathogenic approaches the direction is expected to be from "subpersonal" dysfunctions*
22 *(of genes, brain processes, or cognitive mechanisms) ahead to the resulting phenomenal*
23 *picture. (...) They all see mental pathologies as biomedical entities resulting form a*
24 *dysfunction of physiological processes; hence, the difference is just in the direction of the*
25 *discovery enterprise, i.e., from the syndrome to the underlying pathophysiology in the DSMs,*
26 *from pathophysiology to the resulting syndromes in the etiopathogenic approaches.” [12].*

27 The need for a rethink was also highlighted by Maj’s editorial in World Psychiatry [48] in
28 relation with the article by Cuthbert [18]. Maj stated that *“the gap between the proposed*
29 *dimensions and the signs and symptoms that, as Cuthbert acknowledges, are “the actual*
30 *clinical phenomena that bring patients to the clinic” is sensible in several areas. If the*
31 *problem with the DSM categories may be that they are too distant from the level of*
32 *neuroscience, the problem with at least some of the RDoC constructs may be that they are*
33 *somewhat distant from the level of clinical phenomena” [48].* In fact, Cuthbert in his article
34 did not avoid this issue. He stressed that *“Another issue concerns the relationship of the*

1 various RDoC measures to presenting signs and symptoms, since of course the latter are the
2 actual clinical phenomena that bring patients to the clinic. Establishing mechanistic
3 relationships by which disruptions in the functioning of one or more constructs (as assessed
4 by various Units of Analysis) result in specified symptoms or impairments is considered as a
5 central task for the RDoC project, and a major component of the grant funding program.
6 Notwithstanding the translational research approach, the RDoC project is very much directed
7 toward an understanding of the impairments that patients experience in their lives, and this
8 desideratum was emphasized by the RDoC workgroup in nominating constructs” [18]. Thus,
9 the RDoC project may be seen more as a semiologic project than a nosologic one.

10 The paradigm shift between the RDC and the RDoC is thus a reversal of the link between
11 clinical descriptions of and scientific knowledge about disorders with a view to driving
12 scientific psychiatric medicine forward. Nevertheless, the problem remains as to what signs
13 and symptoms are in psychiatry, and whether semiologic in psychiatry may be considered as
14 an important difference between psychiatric and non-psychiatric disorders. In fact, the
15 theoretical foundations of how semiology was to be incorporated in the DSM-III received
16 very little attention at the time of its conceptualization, and tended to be discussed only
17 subsequently [42, 49].

18 The following section thus describes how signs and symptoms are to be considered in
19 psychiatry. It has been stressed that: “*What the patient manifests is not an isolated series of*
20 *independent referring symptoms/signs but rather certain wholes of interpenetrating*
21 *experiences, feelings, expressions, beliefs, and actions, all permeated by biographical detail.*
22 *These aspects and these wholes are not constituted by a reference to underlying substrate (...)*
23 *but by their meaning* [50]”. Thus, an important question concerning mental manifestations is
24 their coherence. Coherence can be analyzed from an external point of view, which is called
25 explanation or “erklären” by Jaspers. That is: what is the explanation and the mechanism that
26 link together a set of clinical manifestations? The response is here driven by a putative causal
27 substrate. Coherence can also be analyzed from an internal point of view, which is called
28 understanding or “verstehen” by Jaspers [38]. That is: what is the meaning of a set of
29 symptoms for the subject him/herself? The response is driven here by the comprehensive
30 understanding of the individual rather than the symptoms and signs. Indeed, mental
31 manifestations are clearly part of the entire self-experience of the subject, associated with
32 biographical detail and having a personal meaning. This subjective aspect of signs and
33 symptoms has been largely described by phenomenology, for a review, see: [10, 11, 39, 42,
34 49, 51]. The following section mainly deals with the issue of explanation. Two principal

1 points of view are presented: the so-called latent variable model, i.e. the traditional medical
2 one, which considers them as the manifestation of a given underlying pathophysiological
3 mechanism; and the so-called causal network model, i.e. a more psychiatric-specific point of
4 view in which signs and symptoms have their own causal relationship.
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7 *Psychiatric semiology as seen by the latent variable model*

10 Symptoms and signs in non-psychiatric medicine are traditionally considered as an indicator
11 of a latent variable [35]. A latent variable is a variable that is not directly observed but rather
12 inferred from other variables that are observed. This latent variable is taken to be related to a
13 physiological mechanism and thus to be the cause of the semiologic manifestation. Signs and
14 symptoms are considered as independent things - independent from other signs and symptoms
15 and from the context - but are considered to be dependent with regard to the causal
16 physiological substrate that is to be identified.
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18 Two levels of causal physiological substrate and latent variable may be identified, one at the
19 semiologic level and the other at the nosologic level. Signs and symptoms are traditionally
20 considered as manifestations that may be associated with many different disorders.
21 Nevertheless, in non-psychiatric medicine each sign and symptom can be associated with a
22 latent variable that is not a physiological mechanism of the disorder but of the signs and
23 symptoms themselves. We propose to call this latent variable the “distal” latent variable. A
24 distal latent variable may be explained by a different disorder that we propose to refer to as
25 the “proximal” latent variable. The proximal latent variable should explain the occurrence of
26 symptom and signs in a defined disorder, the course of the disorder, its comorbidity, and the
27 treatment response. This distinction between the distal and the proximal is to be found in
28 many fields of medicine. Non-psychiatric semiology has been largely organized until now on
29 the basis of the distal aspects of physiology. The distal is important in any attempt to organize
30 semiologic terminology independently of nosographic issues. To our knowledge, the
31 classification task force of the International League Against Epilepsy (ILAE) is the group that
32 has proposed the best differentiation of the semiologic [52] and the nosographic [53].
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34 The fact that signs and symptoms in psychiatry have not been organized in physiological
35 terms based on the identification of a distal latent variable may be considered as an important
36 difference between psychiatric and non-psychiatric entities. The cause of this putative
37 difference needs to be analyzed thoroughly.
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39 First, for non-psychiatric disorders, a semiologic organization based on neurophysiological
40 factors is possible because of the consensus regarding the framework for classifying
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1 physiological functions. Although the framework is probably not complete, it is sufficient for
2 organizing signs and symptoms on a practical basis. Despite Cuthbert's statement that "*the*
3 *majors systems of the brain have been delineated and related to their functional outputs*"
4 [18], psychiatric semiology may be considered as lacking such a consensual
5 neurophysiological function framework [54]. Thus, symptoms and signs are organized rather
6 according to clinical considerations than physiological ones.

7 Second, the signs and symptoms of non-psychiatric disorders can generally be considered as
8 "objects", i.e. things that are "*publicly accessible and involving mutually independent (and*
9 *typically atomic) entities devoid of subtle or complex forms of meaning, and suitable for*
10 *context-independent definition and measurement*" [39]. In psychiatric semiology, it is more
11 difficult to describe signs and symptoms **solely** as "objects". As Spitzer and Endicott stated in
12 1978, signs and symptoms are "primarily" psychological in nature [21]. This does not mean
13 that signs and symptoms in non-psychiatric disorders are not **subjective**. Indeed, these aspects
14 have already been studied in the field of health psychology [55]. However, it does mean that
15 signs and symptoms in psychiatry should be considered primarily as the manifestations of the
16 modified cognition, emotion and behavior of the patient, leading to a modified inner
17 experience of self, others or the world, and not as the subjective experience of an altered part
18 of the body. **This raises important questions about the means to conduct a reliable and valid**
19 **psychiatric interview (for a review see [50]), about the relationship between semiologic**
20 **psychiatry and the underlying neurophysiological distal mechanism [2] and about the**
21 **formation of mental symptoms [47].**

22 As stated by Kendler: "*a more comprehensive explanation of a psychiatric disorder must*
23 *include an understanding of the production of the key symptoms and signs underlying that*
24 *disorder (...). As we understand the brain processes, we need to "back-translate" the biology*
25 *into an understanding—in psychological terms—of the keys psychopathological constructs*
26 *under investigation*" [2]. **An optimistic and materialist approach could consider that the**
27 **development of cognitive science and neuroscience in the domain of self-experience and**
28 **related physiological mechanisms heralds the possibility of organizing symptoms and signs**
29 **on the basis of physiology.** Chalmers called it a "materialism of type C" [56]. This
30 **materialism posits that if the laws of current physics do not yet allow for the complete**
31 **exploration of mental symptoms, there is no a priori explanatory gap concerning the two types**
32 **of data. The belief is strong that, one day, the development of neurosciences will enable us to**
33 **account entirely for the whole tasting experience strictly in neurophysiological terms.** **A less**
34 **materialist approach, close** to the neurophenomenological project [57, 58], would involve

1 describing signs and symptoms on the basis of their qualitative/subjective aspects and
2 evaluating their neurophysiological correlates on the basis of reciprocal constraints, in which
3 qualitative/subjective aspects and neurophysiological data mutually inform each other [57].
4 “An iterative relationship between psychology and biology, where initial psychological
5 constructs are better defined and subdivided by initial biology findings, which in turn help
6 clarify the biology, will needed to reach a more complete understanding. In short biological
7 and psychological perspectives will coevolve” [2]. The first difficulty of this reciprocal
8 constraint approach is the possibility that symptoms form via different pathways [4, 47].
9 “Because of the different ways in which internal changes can be interpreted, one biological
10 signal can give rise to different mental symptoms. Similarly, it can be envisaged that different
11 biological signals might be configured as the same mental symptom” [4]. The second
12 difficulty is that it supposes that we need to refine the semiologic register in psychiatry [4].
13 As Kendler stressed, “empirical research is crucially dependent on the adequacy of the
14 employed phenotypic distinctions, adequacy that cannot be achieved through a simplistic
15 behaviorist checklist approach” [51]. Berrios also clearly highlighted this issue: “mental
16 symptoms became the “atoms” or “units of analysis” of descriptive psychopathology. This
17 language was calibrated according to the epistemological requirements of contemporary
18 clinical practice and research. Importantly, it has changed little since. (...) Consequently,
19 however, this has resulted in a significant mismatch between the resolution power of the
20 language of psychiatry and that of the instruments devised to capture and measure its proxy
21 variables” [4].
22 In line with the DSM-III position, psychiatric signs and symptoms are primarily mental and a
23 rigorous methodology is required to organize them in psychiatric semiology and to obtain a
24 reliable neuroscientific explanation for them [42, 43, 49, 51]. A challenge in psychiatry is
25 thus to better define and organize a patient’s symptoms and signs in terms both of his/her
26 subjacent brain mechanisms and of his/her inner experience of the symptoms and signs
27 (according to a reciprocal constraint approach).

29 *Psychiatric semiology as seen by the causal network model*

30 The previous latent variable model of semiology posited that symptoms and signs are
31 independent things related together by a latent variable [59]. However, it has also been
32 suggested that symptoms and signs have properties with autonomous causal relevance [60].
33 “Instead of being effect of common cause, psychiatric symptoms have been argued to cause
34 each other” [59]. Thus, symptoms and signs can be related by causal chains that can be better

1 studied by a causal network model. This network approach considers symptoms and signs as
2 “nodes” and causal interactions between symptoms as “connections between nodes”.
3 According to this point of view, a psychiatric disorder is to be considered as a set of
4 symptoms and signs that are connected through a system of causal relations [61]. *“In such a
5 model, symptoms are not an indicator of an underlying pathological process, rather they are
6 parts of a functionally interconnected causal network”* [62].

7 From a clinical point of view, the causal network model helps the psychiatrist in collecting
8 signs and symptoms. Thus, collection is not solely based on the search for a latent
9 physiological mechanism that might explain the manifestation but also on the understanding
10 of the relationship between the symptoms and signs in the experience of the subject [39, 59].

11 Indeed, psychiatrists intuitively interpret relations between symptoms as causal networks
12 [63]. For example, the relationship between hallucination, anxiety and insomnia is
13 understandable through their causal relationship without any need for a latent variable.
14 Interestingly, the DSM itself contains criteria with causal relationships, e.g. for the panic
15 disorder: worries about the possible implication of another attack [63], or for the obsessive-
16 compulsive disorder: compulsion in response to an obsession [59]. However, a limitation of
17 the causal network model is that it is elusive about what symptoms or signs are to be included
18 in the model. Mental symptoms and signs remain the “units of analysis” but their nature,
19 formation and how they are to be captured are not clearly defined [38]. Nevertheless, the
20 semiologic register in psychiatry is not a simple and neutral “description” of reality [4]. It
21 construes mental manifestations in particular ways, a point that has received very little
22 attention in the psychiatric literature on the causal network model. Yet this approach could be
23 of interest to better describe the formation of psychiatric manifestations. Indeed, such a
24 network approach model can include social interactions [64] and their impact on the
25 formation of mental symptoms and signs. As Berrios highlighted, *“the final description of
26 symptom results from the interaction between a tenuous biological signal (originated in an
27 affected brain site) and the layers of psychosocial codes (noise) partaking in the process of
28 symptom formation. (...) The crucial point here is that clinical ‘observation’ is never a
29 cognitively innocent activity”* [5]. This view is known as the Cambridge model of symptom
30 formation [4, 47], which is related to the hypothesis that the biological/physiological signal
31 (related to a brain modification) is something pre-linguistic and pre-conceptual (also called
32 the “primordial soup”[47]) that needs to be constructed to be communicated according to
33 social configurators (**Figure 1**) [65]. Further work could investigate how such configurators
34 could be included in the causal network model.

1 From a physiological point of view, the causal network model is agnostic with regard to how
2 causal relations between symptoms and signs are grounded [59]. However, it involves
3 considering the mechanism underlying the clinical psychiatric manifestation not in terms of a
4 single clear explanation but rather as a multifactorial entity, as with the systemic biological
5 approach to brain functioning [26]. **Figure 1.** The way in which the psychiatric disorder
6 develops into a set of symptoms and signs that are relatively stable may be related to the
7 process regulating homeostatic brain function. They are more or less stable because they
8 reinforce each other mutually and because such a network may be subsumed by brain
9 homeostatic regulation underpinned by complex and mutually reinforcing networks of causal
10 mechanisms. **Figure 1.** This implies adding a semiologic level to the traditional multilevel
11 analysis in neuroscience. Interestingly, such a semiologic view would involve identifying not
12 only clearly defined signs and symptoms but also “anti-signs” and “anti-symptoms” that
13 “*protect against disorder by blocking the spreading of problems through the network*” [60].
14 The fact that signs and symptoms in psychiatry are neither independent nor passive could be
15 considered as an important difference between psychiatric and non-psychiatric entities.
16 **Indeed, the model has also been called the “network approach to psychopathology” [59].**
17 **However, the causal network model has also been applied to non-psychiatric disorders, in line**
18 **with the concept of “diseasome” [66] and “network medicine” [64, 67]. However, in such a**
19 **model, nodes represent “disorders” and not “symptoms and signs”. To our knowledge, the**
20 **causal network model has not been used for the symptoms and signs of non-psychiatric**
21 **disorders. Nevertheless, the model has been applied to health-related quality of life in healthy**
22 **adults and patients with cancer [68], which highlight the interest of such an approach in the**
23 **domain of chronic diseases to better understand the impact and the relationship of cognition,**
24 **emotion and behavior on patients’ health [69].**
25 The absence of a single latent variable or the absence of a common cause could mean that it is
26 impossible to establish a **pragmatic measure of explanation in line with the complexity and**
27 **the multilevel characteristics of the model.** In fact, a “network model load” could be measured
28 **and would prove very useful in clinical practice and research.** Indeed, multilevel causal chains
29 cutting across levels of organization and timescales can be projected in lower dimensional
30 space. The key challenge is to find the lowest dimensional denominator that explains the
31 behavior of the system and then to extract a metric that is relevant in both nosologic and
32 semiologic terms. **Figure 3** provides two examples in which a unidimensional view based on
33 averages does not meaningfully differentiate controls and patients, whereas a
34 multidimensional view allows a problem to be encompassed by a compound metric separating

1 the two populations. Recent development in machine learning has boosted the use of such
2 multivariate metrics but they still need a clear evaluation of their validity in relation to
3 physiological mechanisms. Evaluation of their reliability is more complex and can even
4 question existing boundaries. The recent development of normative modeling, for instance,
5 makes it possible to move away from a traditional case vs. control approach and to consider
6 more complex scenarios with various spectra and comorbidities [70].

7 A challenge in psychiatry is thus to incorporate the semiologic more meaningfully into a
8 consensual network model that combines social interaction (including with the medical
9 system), psychological processes, neuronal functioning and even genetic data [71]. As we
10 have underlined, the RDoC is based on an integrative, multilevel, multisystem approach. We
11 think that research in semiology should form part of the RDoC project in order to better
12 understand the link between brain dysfunction and the clinical manifestations of disorders
13 [20]. This would link in much better with clinical practice. Nevertheless, two major
14 challenges remaining are: i) to train the new generation of psychiatrists in how such an
15 interdisciplinary perspective may be adopted, and ii) to include digital technology in their
16 training in order to optimize the delivery of psychiatric medicine in the future [71, 72].

1 **Conclusion**

2 This article questions the notion that psychiatric disorders are to be considered differently
3 from non-psychiatric disorders. We have shown that debate until now has focused more on
4 the nosologic than on the semiologic. Rather than highlighting specific features of psychiatric
5 disorders, nosologic point of view reveals factors that co-occur across the entire field of
6 medicine if the objective is to establish the boundaries between the normal and the pathologic
7 and between different disorders. Psychiatry is thus very important in medicine because it
8 exemplifies the inherent problem of the construction of a cognitive framework that has been
9 imposed on clinical and scientific medical information to delineate a classification of
10 disorders and to increase its comprehensibility and utility. In this sense, it can be considered
11 that psychiatric disorders are not different from non-psychiatric disorders, provided that care
12 is taken in how non-psychiatric disorders are defined. This paradigm shift is in line with the
13 position of Spitzer and Endicott in 1978 when they stated that “*a mental disorder should be*
14 *defined as merely a subset of medical disorder, and that our attention should therefore be*
15 *directed toward defining the broad rubric of medical disorder*” [21]. Thinking about
16 psychiatric classification should therefore seek to “*clarify the goals of medical classification*”
17 and offer “*a rationale for decisions as to which consideration should be included or excluded*
18 *from a medical classification*” [21].

19 In contrast, semiologic point of view has led to the discovery of psychiatric features that
20 underline the great value of psychiatry and the scientific challenges it faces. This position is
21 in line with Berrios who claims that the “primary objects” of psychiatry are mental symptoms
22 and signs, and that mental disorders are “derivative objects”, with higher level organizations
23 [47]. This article has focused on the need to better define and classify signs and symptoms in
24 psychiatry based on a dual, mutually interactive biological and psychological perspective and
25 to incorporate semiologic psychiatry into a multilevel multisystem brain/cognitive approach.
26 In such a view, there is an urgent need to “*make semiologic psychiatry great again*”. As for
27 nosologic issues, an international task force should be set up to investigate semiologic
28 psychiatry in the field of medicine. In this task force, historical, societal, epistemological and
29 phenomenological (in its continental philosophical meaning [10]) aspects concerning mental
30 manifestations discussed in this article should be not forgotten. Moreover, as chronic disease
31 becomes an ever greater burden for society [72], such a task force would have a great effect in
32 better understanding the impact of cognition, emotion and behavior on the onset and
33 maintenance of non-psychiatric disorders beyond the dichotomy between mental and physical
34 disorders.

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1 **Table 1:** The Spitzer & Endicott 1978 criteria regarding the boundaries between the normal
 2 and the pathologic [14].

3

All four criteria, A through D, must be met for a condition to be designated as a medical disorder.

Criterion A. The condition, in the fully developed or extreme form, in all environments (other than one especially created to compensate for the condition), is directly associated with at least one of the following:

1. **distress**—acknowledged by the individual or manifested;
2. **disability**—some impairment in functioning in a wide range of activities;
3. **disadvantage** (not resulting from the above)—certain forms of disadvantage to the individual in interacting with aspects of the physical or social environment because of an identifiable psychological or physical factor. The following forms of disadvantage, even when not associated with distress or disability, are now considered, in our culture, as suggestive of some type of organismic dysfunction warranting the designation of medical disorder:
 - a. impaired ability to make important environmental discriminations (e.g., color blindness, lack of pain perception).
 - b. lack of ability to reproduce (e.g., sterility).
 - c. cosmetically unattractive because of a deviation in kind, rather than degree, from physical structure (e.g., fused toes).
 - d. atypical and inflexible sexual or other impulse-driven behavior which often leads to painful consequences (e.g., sexual sadism, kleptomania, pathological gambling).
 - e. impairment in the ability to experience sexual pleasure in an interpersonal context (e.g., fetishism).
 - f. marked impairment in the ability to form relatively lasting and non-conflictual interpersonal relationships (e.g., narcissistic and hysterical personality disorders).

Criterion B. The controlling variables tend to be attributed to being largely **within the organism** with regard to either initiating or maintaining the condition. Operationally, this criterion is determined by the following: A condition is included [as a disorder] only if it meets both of the following criteria:

1. **Simple informative or standard educational procedures** do not lead to a reversal of the condition.
2. **Nontechnical interventions do not bring about a quick reversal of the condition.**

Criterion C. Conditions are not included if the associated distress, disability, or other disadvantage is apparently the necessary **price associated with attaining some positive goal**.

Criterion D. Distinctness from other conditions in one or more of the following features: **clinical phenomenology, course, response to treatment, familial incidence, or etiology**.

4

5

1 **Table 2:** Operational criteria for setting the boundaries between the normal and the
 2 pathologic in the DSM III, IV and 5.

3

DSM	“Inclusion criteria” to identify signs and symptoms that will be considered as “clinically significant”	“Exclusion criteria” to identify signs and symptoms that will not be considered as pathologic
DSM-III	“In DSM-III each of the mental disorders is conceptualized as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is typically associated with either a painful symptom (distress) or impairment in one or more important areas of functioning (disability) ”.	“In addition, there is an inference that there is a behavioral, psychological, or biological dysfunction, and that the disturbance is not only in the relationship between the individual and society. (When the disturbance is limited to a conflict between an individual and society, this may represent social deviance, which may or may not be commendable, but is not by itself a mental disorder.)”.
DSM-IV	“In DSM-IV, each of the mental disorders is conceptualized as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom ”	“In addition, this syndrome or pattern must not be merely an expectable and culturally sanctioned response to a particular event, for example, the death of a loved one. Whatever its original cause, it must currently be considered a manifestation of a behavioral, psychological, or biological dysfunction in the individual. Neither deviant behavior (e.g., political, religious, or sexual) nor conflicts that are primarily between the individual and society are mental disorders unless the deviance or conflict is a symptom of a dysfunction in the individual, as described above.”
DSM-5	“A mental disorder is a syndrome characterized by clinically significant disturbance in an individual’s cognition, emotion regulation, or behavior (...). Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities ”.	The signs and symptoms should “reflect a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. (...) An expectable or culturally approved response to a common stressor or loss, such as the death of a loved one, is not a mental disorder. Socially deviant behavior (e.g., political, religious, or sexual) and conflicts that are primarily between the individual and society are not mental disorders unless the deviance or conflict results from a dysfunction in the individual, as described above.”

4

1 **Table 3:** Validity criteria to classify different disorders

2

References	Validity criteria
Robin and Gruze criteria 1970 [30]	<ol style="list-style-type: none"> 1. Clinical description 2. Laboratory study 3. Delimitation from other disorders 4. Follow-up study 5. Family study
Spitzer and Endicott 1978 [14]	<ol style="list-style-type: none"> 1. Clinical phenomenology 2. Course 3. Response to treatment 4. Family incidence 5. Etiology
Kendler criteria 1990 [26]	Robin and Gruze criteria +
DSM-5 criteria 2013 [13]	Differential response to treatment <ol style="list-style-type: none"> 1. Shared neural substrates 2. Family traits 3. Genetic risk factors 4. Specific environmental risk factors 5. Biomarkers 6. Temperamental antecedents 7. Abnormalities of emotional or cognitive processing 8. Symptom similarity 9. Course of illness 10. High comorbidity 11. Shared treatment response
RDoC criteria [18]	<ol style="list-style-type: none"> 1. Inventory of brain functions 2. Inventory of brain dysfunction: <ol style="list-style-type: none"> a. the related phenomenological expression b. the mechanism of dysfunction (integrative and multisystem point of view)

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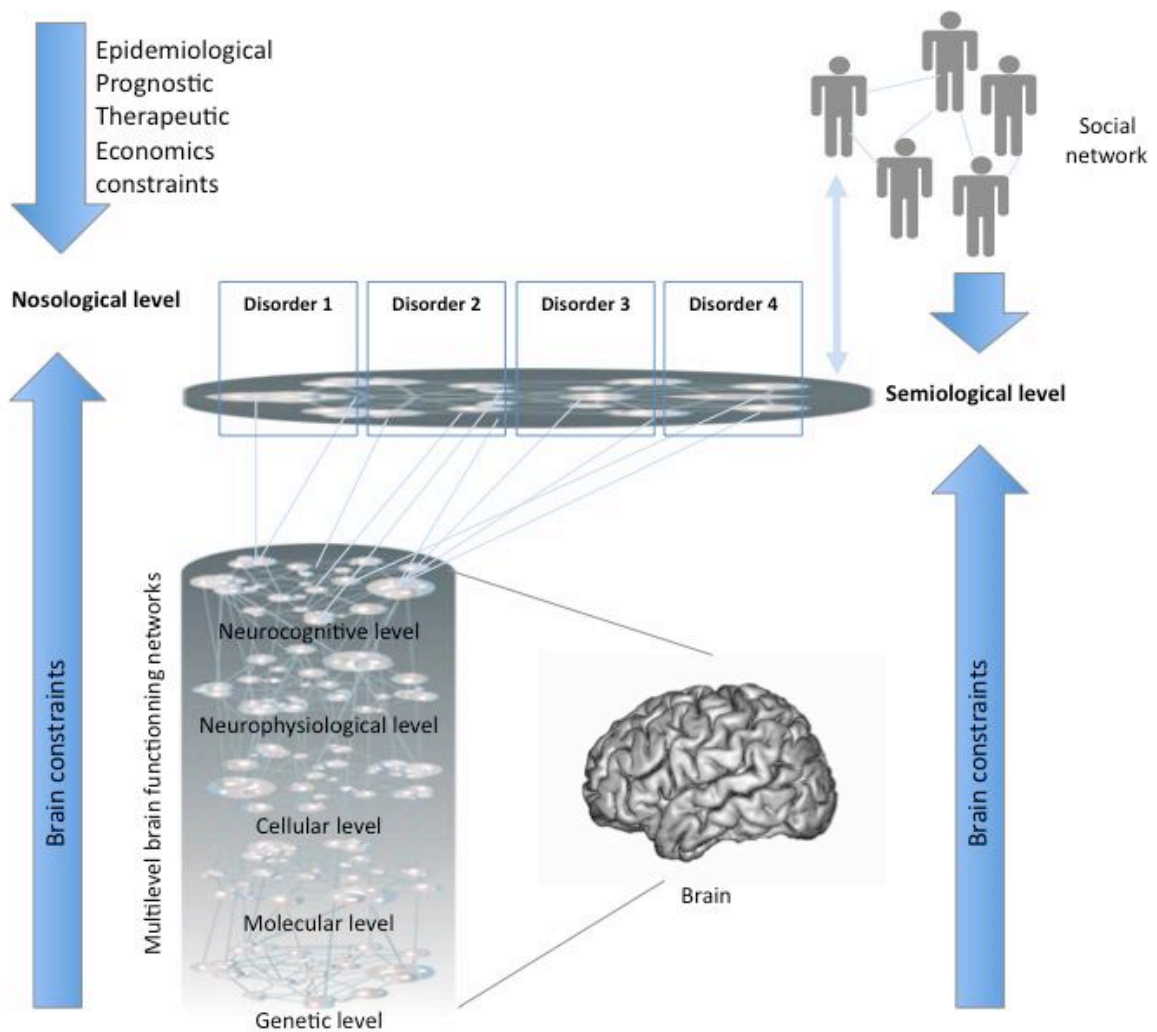
1 **Figure 1**

2 Proposition for framework to better identify nosologic and semiologic issues in psychiatry.

3 Left part of the figure: delimiting psychiatric disorders (nosologic level) is not only based on
4 brain constraints that reflect pathophysiological mechanisms, but also on the semiologic level
5 and on epidemiological, prognostic, therapeutic and economic factors [27].

6 Right part of the figure: adaptation of the Cambridge model of symptom formation [47],
7 which posits that mental manifestations, i.e. the semiologic level, result from interactions
8 between brain constraints and social constraints, which in turn are related to the formation and
9 expression of symptoms and signs within a social network.

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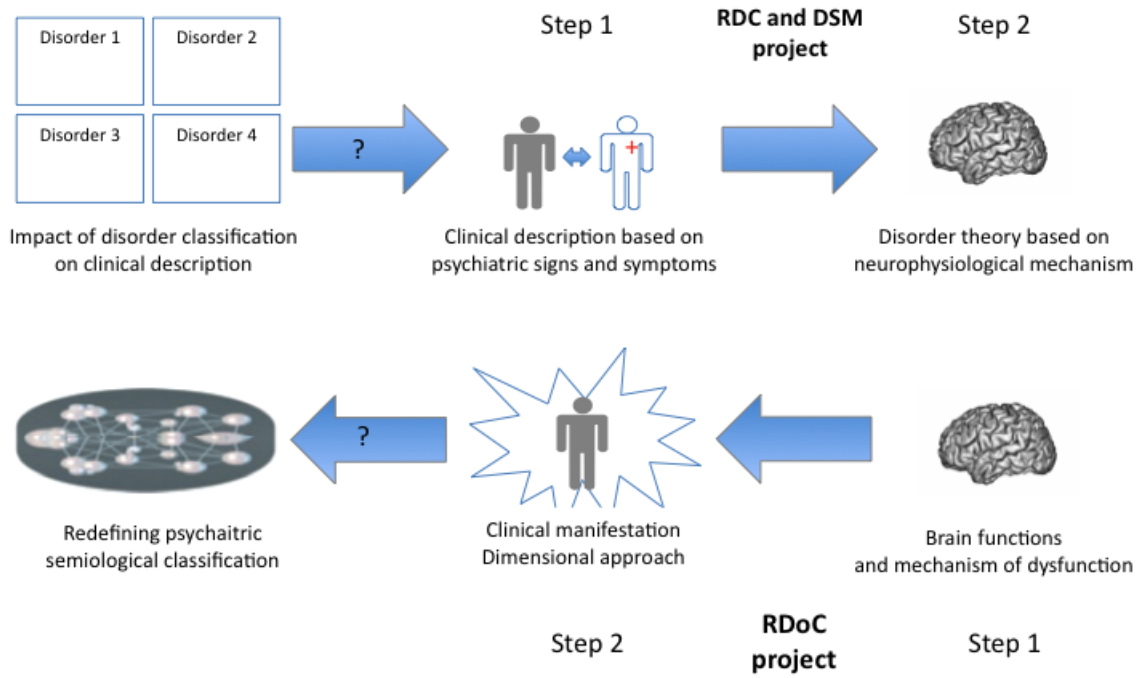


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1 **Figure 2**

2 Relation between semiologic psychiatry, RDC/DSM project and RDoC project [12].

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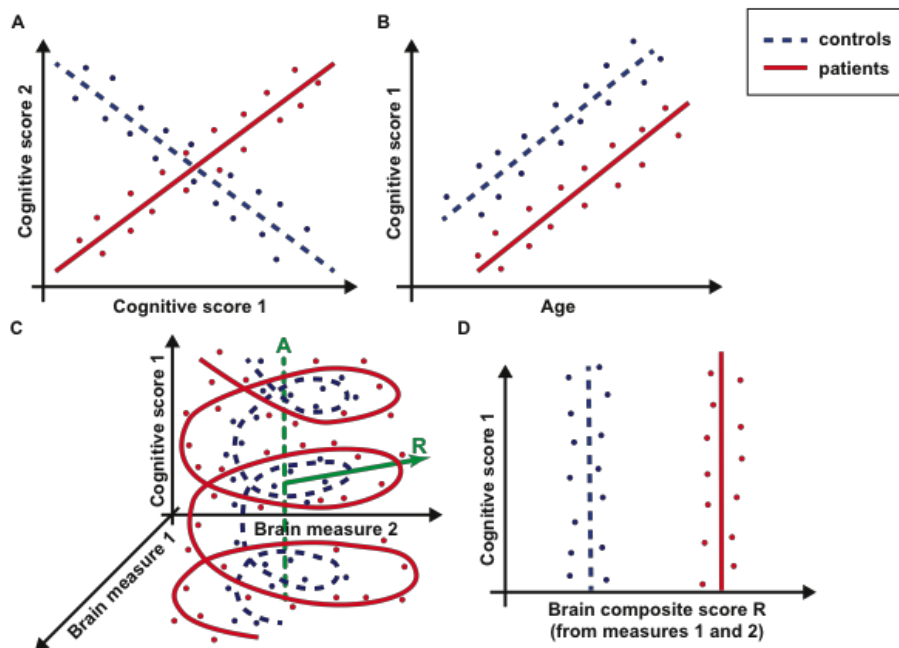
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1 **Figure 3**

2 Sometimes, one need to use multi-dimensional spaces to be able to find a simpler
3 unidimensional metric. A, B) two common cases where two variables can be simplified into
4 one metric: A) interaction between cognitive scores 1 and 2 and B) offset in the cognitive
5 score 1 compared to cognitive score 2. Difference between groups remains hidden when
6 averaging across the age dimension; C) example of a more complex landscape with helicoidal
7 trajectories in three dimensions. The two brain measures can be reduced to a unidimensional
8 composite score by calculating the distance R between each participant and the axis A. D)
9 The new composite score better explains the separation between the groups.



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