Can psychopathology and neuroscience coexist in psychiatric classifications?

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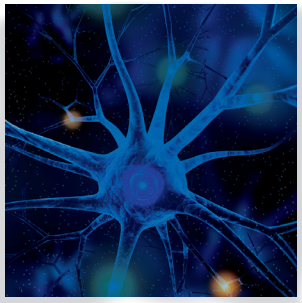

A crisis of confidence was triggered by the disappointment that diagnostic validity, an important goal, was not achieved with the publication of Diagnostic and Statistical Manual of Mental Disorders (DSM-5). *The Research Domain Criteria (RDoC) project, which provides a framework for neuroscientific research, was initially conceptualized as an alternative to* DSM. *However, RDoC and* DSM *are complementary rather than mutually exclusive. From a historical perspective, this article argues that the debate opposing psychology and brain in psychiatric classification is not new and has an air of déjà vu. We go back to the first classifications based on a scientific taxonomy in the late 18th century with Boissier de Sauvages, which were supposed to describe diseases as they really existed in nature. Emil Kraepelin successfully associated psychopathology and brain research, prefiguring the interaction between* DSM *and RDoC.* DSM *symptoms remain valuable because they are the only data that are immediately and directly observable. Computational science is a promising instrument to interconnect psychopathological and neuroscientific data in the future.*

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DSM vs RDoC?

This article is part of an issue of *Dialogues in Clinical Neuroscience* that is devoted to current controversies in psychiatry. Over the last decades, the psychiatric community has been agitated by renewed doubts about the utility of our current diagnostic classifications. This "validity crisis" culminated when the publication of *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* was greeted by the concurrent announcement of the Research Domain Criteria (RDoC)[1] project by the NIMH. The RDoC project aims at providing a framework for translational research into several domains (negative valence, positive valence, cognitive systems, social process, arousal and modulatory systems) at several levels of analysis (genes, molecules, cells, circuits, physiology, behaviors, self-report, paradigms). With respect to *DSM*, the RDoC project was initially perceived as a rival claim to the throne rather than a joint effort. Criticism of *DSM* focused on the heterogeneity of numerous categories, which was cited as a major hindrance for research. It is true that the obvious diversity of patients recruited on the basis of, say,

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DSM-5 criteria for Major Depressive Disorder (MDD) or Posttraumatic Stress Disorder (PTSD), is likely to have contributed to the inconclusive results of many drug trials. In parallel to the heterogeneity within categories, a categorical classification is not ideally suited to conducting research on dimensional or trans-diagnostic traits that may be common to different clinical entities. The object of the debate is now whether our current diagnostic categories, as defined by *DSM-5*, and soon by the *International Classification of Diseases (ICD-11)*, are still useful, or should they be discarded? In that case, is there a meaningful alternative? Should we: (i) remain faithful to *DSM*, (ii) embrace RDoC totally, or (iii) try to reconcile both? Psychiatry's history—both recent and remote—suggests that the last proposition is the only viable one. The debate about the basis of classifications—ie, whether classifications should be descriptive, or whether they should be based on an etiological theory—has resurfaced whenever psychiatric knowledge was at a critical juncture or made new leaps.

Proximal roots of the current validity crisis

We may summarize the recent events in psychiatry by stating that *DSM-III* introduced *reliability*, in the form of a common vocabulary, after the era of psychoanalysis and antipsychiatry (both of which did not view classification as primordial). Clinicians and scientists supposed that this newly restored reliability was the long-expected prerequisite that would pave the way for future research, ultimately leading to validity. The current crisis of confidence was triggered by the disappointment that diagnostic validity, an important goal, was not achieved with the publication of *DSM-5*, despite optimistic promises and high expectations. In order to enhance validity, many proposals were circulated during the preparatory phase of *DSM-5*. One such suggestion was to rely more on dimensions and less on categories. However, dimensions were ultimately rejected because they were perceived as too cumbersome for use in everyday clinical practice; as is well-known, the dimensional model of personality was finally relegated to Section III. Another idea was to select markers derived from the wealth of data contributed by the very productive research into genetics, brain imaging, neurocircuitry over the last two decades. The Research Agenda for *DSM-5*, published in 2002, contained a proposal by Charney et al[2] for a possible multiaxial system capable of accommodating neuroscientific parameters (Axis I: Genotype [eg, genes related to disease, resiliency, or therapeutic response]; Axis II: Neurobiological phenotype [eg, neuroimaging, cognitive functions, emotional regulation]; Axis III: Behavioral genotype; Axis IV: Environmental modifiers or precipitants; Axis V: Therapeutic targets and response). After the abandonment of dimensions and biological markers, the publication of *DSM-5* in 2013 certainly gave us a very valuable instrument. However, disappointment was felt because the final product did not correspond to the paradigm shift that had been promised, and disappointment unleashed criticism.

What is a good classification?

Classifications are primarily judged according to their reliability and validity. In addition, they should be useful and practical. *Validity* means that our diagnostic categories describe real entities and not flawed concepts. This is a difficult endeavor if we take into account that we still ignore the etiology of most psychiatric disorders. Robins and Guze[3] proposed a five-phase method for achieving diagnostic validity including: (i) clinical description; (ii) laboratory studies; (iii) delimitation from other disorders; (iv) follow-up studies; and (v) family study. Step 3 is traditionally a cornerstone of classification; it postulates that a diagnostic category should be homogeneous, and that "patients with other illnesses are not included in the group to be studied." A cognate concept is that a valid diagnostic category should have distinct boundaries and should be separated both from normality and from other diagnostic categories by a "zone of rarity." For example, PTSD should be distinct from the normal response to adversity, and patients with PTSD should not usually have major depression or anxiety disorders.[4] More refined procedures to guarantee validity have been proposed more recently. Kendler[5] differentiated antecedent, concurrent, and predictive validators. Andreasen[6] suggested validators contributed by findings from genetics, neurochemistry, neuroanatomy, neurophysiology, and cognitive neuroscience. Andreasen's proposals look like a harbinger of RDoC's units of analysis. Validity is not the sole requirement, and other qualities such as utility[7] and complexity[8] also must be taken into account. Utility designates the practicable information that is conveyed by the diagnosis in terms of treatment planning, outcome, and sometimes etiology. An ideal classification should also be able to

cope with the complexity of psychiatric disorders, which refers to the multiple reciprocal interactions between the various etiological factors.

Finally, classifications have to cope with the necessity to accommodate a large spectrum of disorders, ranging from quasi-neurological diseases to ailments that are heavily influenced by psychosocial factors. At the extreme, because of reimbursement issues, classifications have to provide diagnoses for normal persons who consult psychotherapists to sort daily life problems. Interestingly, in his *General Psychopathology (Allgemeine Psychopathology)*, published in 1913, exactly 100 years before *DSM-5* and RDoC,[9] Karl Jaspers proposed that some psychiatric disorders followed the traditional medical model, whereas other psychiatric disorders, such as abnormal reactions or neurotic syndromes, were not medical disorders but variations of normality, which he placed in a so-called "Group III."

Finally, a classification should be meant for the whole international scientific community and not confined to a country. This does not go without saying. Indeed, a study[10] showed that France was one of the few countries where more than 30% of clinicians felt the need for a national classification of mental disorders (along with Cuba, Russia, India, Japan, and the People's Republic of China) whereas less than 5% of interviewed persons shared this need in other European countries (eg, Germany, Spain, or the United Kingdom). A revised version of the *Latin American Guide for Psychiatric Diagnosis (GLADP-VR)*[11] was published in Spanish in 2012, and a revised French Classification of Mental Disorders[12] in 2015.

It is very simple: we do not know what the universe is

The main obstacle to validity is the sad fact that we ignore the ultimate causation of most mental disorders. In 1952, the Argentine writer Jorge Luis Borges[13] described a fictitious Chinese encyclopedia, entitled "Celestial Empire of Benevolent Knowledge" that classified animals as follows: (a) belonging to the emperor; (b) embalmed; (c) tame; (d) suckling pigs; (e) sirens; (f) fabulous; (g) stray dogs; (h) included in the present classification; (i) frenzied; (j) innumerable; (k) drawn with a very fine camelhair brush; (l) et cetera; (m) having just broken the water pitcher; (n) that from a long way off look like flies. These categories are not mutually exclusive. For instance, a Chinese emperor might own a tame suckling pig, and ask a scribe to trace his name with a delicate camelhair brush. Though tame, this piglet, still young and playful, might one day shatter the water pitcher when gamboling. Obviously, the suckling pig is included in this classification (h), which means that the young animal would finally qualify for categories a, c, d, h, k, and n. This is an image of the comorbidity that afflicts *DSM-III, -IV* and *-5*. Borges used the system devised by this apocryphal Chinese encyclopedist to illustrate the point that every classification in the universe is "arbitrary and full of conjectures." Most importantly, he further stated that "the reason for this is very simple: we do not know what the universe is." ("La razón es muy simple: no sabemos qué cosa es el universo"). It is true that we know little about the etiology of mental disorders, and to cut a long story short, that's why we are stuck with our diagnostic categories. In spite of that, Borges' definition would boast correct reliability (if we were to use it, most of us would classify various animals in the same way).

There is nothing new under the sun

An examination of the early history of psychiatry suggests that the controversy about nosology, ie, the debate about whether classifications should be based on observable symptoms or on putative etiologies, is considerably older that the rift between *DSM* and RDoC. J. de Leon described the current debate as a feeling of déjà vu after 100 years.[14] We may therefore conjecture that this debate is long-lasting and inherent to our discipline.

At the juncture between the epochs known as the Scientific Revolution and the Enlightenment, the first modern medical classifications were based on the system of scientific taxonomy developed by Carl Linnaeus (1707–1778). Boissier de Sauvages (1706–1767) maintained correspondence with him. He used Latin to compile his "Methodical Nosology" (1763), a systematic classification of all known diseases (2400 individual diseases), "in accordance with the method of Thomas Sydenham and Linnaean taxonomy."[15] The foreword to the posthumous French edition (1771) explains that observable features that exist only in the given disease, and distinguish it from all others, designate each disease. It was assumed that diseases could be captured as they existed in nature, and that "zones of rarity" separated them from one another. In Boissier de Sauvages' nosol-

ogy (*Table I*),[16] mental illnesses (Vesaniae) made up the 8th class of diseases; they were divided into four orders (Hallucinations, Morositates, Deliria, Folies anomales). Each order comprised several illnesses that were further subdivided into various types. *Table I* shows that each group comprises illnesses that are postulated to be caused by a common mechanism; an exception is the 4th order that seems to be a residual category (a kind of "Not Otherwise Specified" box).

The Encyclopedia compiled by Diderot and d'Alembert, the most influential publication of the Enlightenment, had an entry about "nosology" that was written in 1765 by Jean Joseph Menuret de Chambaud (1739-1815), a physician interested in the fields of semiotics and mental illnesses. As an adept of "neo-Hippocratism," he believed that a physician should follow the method of directly observing the facts and should not get misled by theories. Menuret writes in the Enyclopedia that illnesses can be classified only according to their symptoms, since the knowledge acquired from the etiologies is always uncertain because it is speculative. Therefore, Menuret states that nosology should be simply equated with symptomatology. In his words, this approach is similar to the method used by the natural-

Class VIII. VESANIAE (Insanities)	
Order I. HALLUCINATIONS	***Caused by disturbances of organs outside the brain, with the result that imagination is misled***
Vertigo	Outside objects are seen as twirling
Suffusio	Seeing objects that do not exist
Diplopia	One object is seen as double or multiple
Syrigmus	Hearing a noise in the ear, even though there is no noise outside
Hypochondriasis	The postulated mechanism is that patients are hallucinating about their health
Somnambulism	Also conceptualized as a hallucination
Order II. MOROSITATES	***"Bizarreries." Perverted desires or aversions***
Pica	Aversion to usual food, and appetite for non-nutrient substances
Bulimia	Eating more than one can digest
Polydypsia	Drinking more than necessary
Antipathia	Aversion to particular objects
Nostalgia	Illness caused by a violent desire to see one's relatives or home country
Panophobia	Groundless fear
Satyriasis	Excessive sexual desire in the male, with priapism
Nymphomania	Uncontrollable sexual desire, in a woman
Tarantism	Extreme impulse to dance
Hydrophobia	Excessive aversion to water, most often because of being bitten by a rabid animal
Order III. DELIRIA (Delusions)	***Caused by an abnormality of the brain***
Paraphrosine	Temporary delusional state caused by a substance or a medical illness
Amentia	"Universal" delusional state without furor (i.e. without mania)
Melancholia	"Partial" and nonaggressive delusional state with sadness and chronicity
Mania	"Universal" delusional state
Daemonomania	Melancholia attributed to the devil
Order IV. ANOMALAE VESANIAE (Anomalous Insanities)	
Amnesia	Total loss of memory
Agrypnia	Insomnia

Table I. Mental disorders in Boissier de Sauvages' Methodical Nosology (1763).

ist who creates a solid and clear classification of plants on the basis on the visible shape of fruits, flowers and leaves, instead of basing his system on the intimate structure of plants as seen with a microscope.

This botanical taxonomy, which was supposed to describe real diseases as present in nature, was demolished by Philippe Pinel (1745–1826), who criticized Boissier de Sauvages for his arbitrary choices, for mistaking isolated symptoms for proper illnesses, and for unduly expanding the number of categories (the same criticism was also made of *DSM*). Pinel[17] narrated that he decided to disregard theoretical classifications and to rely on his own observations. Interestingly, Emil Kraepelin broke with the past in a similar way, and decided, after reproducing published knowledge in the first editions of his textbook, that it was time to start constructing a new system based on his own data ("Krankheitsbilder"). Kraepelin was painfully aware that his diagnostic categories were only syndromes ("Symptomenkomplexe") and that the state of science did not yet allow him to describe real diseases ("Krankheitsformen"). In the very first edition of his textbook (1883), then called Compendium, Emil Kraepelin wrote "These syndromes will only acquire a deeper scientific basis when we will be able to establish that each of them has an understandable relationship with abnormalities of the brain cortex." („Eine tiefere pathologische Begründung werden diese Symptomenkomplexe erst dann gewinnen, wenn es gelingt, ihre gesetzmäßige Abhängigkeit von krankhaften Störungen der Hirnfunktionen im einzelnen nachzuweisen.")

At a time when we are learning how to derive the best from both *DSM*-5 and RDoC, Kraepelin remains a guiding figure. He was confronted with a concurrent school of all-brain nosology, but he combined different currents within a non-dogmatic and flexible frame. In fact, before RDoC, there has been a previous endeavor to map mental illnesses on the brain. Theodor Meynert (1833-1892) in Vienna was the first major representative of that current. Under his influence, his brilliant young student, Carl Wernicke (1848-1905), pursued the idea of localizing various brain lesions and deducing their clinical consequences. Wernicke published his seminal article on aphasia in 1874 when he was just 26 years old.[18] It took Meynert 10 more years (1884) to publish a book with the revealing title: "Psychiatry; clinical aspects of the illnesses of the forebrain." Arthur Schnitzler and Sigmund Freud were residents in Meynert's clinic but, as is known, they decided to follow a different path. As Kendler[19] wondered, "What if Wernicke, the one genuine competitor with Kraepelin for prominence in German psychiatry at the turn of the 20th century, had not died from a bicycle accident at the age of 52 in 1905?" Nevertheless, Kraepelin held Wernicke in high esteem,[20] and he recruited a few of his disciples (eg, Robert Gaupp in Munich, or Karl Ludwig Bonhoeffer as successor in Heidelberg). Kraepelin knew that his nosological system was temporary and was bound to incorporate new data and undergo transformation. Even though Kraepelin thought that brain pathology was not advanced enough in his times to sustain a valid nosological classification, he consistently tried to connect psychopathology and brain pathology. When that became possible, he attracted the best brain pathologists to his clinic (Alzheimer, Nissl, Spielmeyer, and Brodmann) and the successive editions of his textbook contained precise descriptions of brain research.[21]

The way forward is reconciliation

Even though *DSM* and RDoC have been viewed as antagonistic, most clinicians would consider today that they are complementary and synergistic approaches. The title of this article is a controversial question—can psychopathology and neuroscience coexist in psychiatric classifications?—that, in our opinion, can be answered most positively.

Jablensky[22] recently expressed the thoughtful opinion that the way forward will be found in the conceptual reconciliation of both approaches. Realistically, we cannot function without a *DSM*-like classification. Clinicians prefer diagnostic categories, even though they are aware that categories are not valid in the sense that they are not discrete, and that they are only concepts and not real entities. However, diagnostic categories possess "utility" by virtue of the practical information they convey about treatment strategy and because they can be used for effective communication and decisions. On the other hand, the RDoC project is fascinating. It has been dubbed a "promissory note" and, in all likelihood, the note will be honored in a sumptuous manner, even though the period of time is unknown. RDoC has attracted considerable interest as a research framework. A March 2017 search of the NIH Reporter engine returned over 300 hits for funded research grants with "RDoC" as a search term, almost all in the clinical/translational area.

Also, the growth of computational science, and the ability to handle and decipher voluminous amount of data, will probably facilitate the integration of *DSM* and RDoC. DSM symptoms remain valuable in research because they are the only elements that we can observe directly. Strategies for the formal integration of *DSM* categories and RDoC dimensions have been delineated, for instance in a paper whose last author is Joshua A. Gordon, the current director of the National Institute of Mental Health.[23] This paper discusses mathematical models where pathophysiological mechanisms, hidden from direct observations, may be inferred from their observed outcomes (ie, *DSM* symptoms and diagnoses, that are treated as observations).

Another reason to keep *DSM*, while making the most out of RDoC, is to break the pattern of destructive "wipeouts" in psychiatry described by Edward Shorter, a renowned historian of psychiatry. In lectures on "The fragility of psychiatric knowledge,"[24] Shorter reminds us that psychiatry is the only medical specialty that has endured two "total knowledge wipeouts." In the 1920s, the triumph of psychoanalysis wiped out the previous century of research in biological psychiatry. Psychoanalysis was similarly displaced by the return of biological thinking in psychiatry in the 1970s. As a mature discipline, psychiatry should be able to admit change without breaking, keeping up with the pace of neuroscientific research without throwing overboard centuries of precious psychopathological knowledge. ❑

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¿Pueden coexistir la psicopatología y las neurociencias en las clasificaciones psiquiátricas?

El que no se haya cumplido el importante objetivo de la validez diagnóstica con la publicación del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-5), ha provocado decepción y una crisis de confianza. El proyecto Research Domain Criteria (RDoC), que proporciona un marco para la investigación neurocientífica, se conceptualizó inicialmente como una alternativa al DSM. Sin embargo, RDoC y DSM son complementarios en lugar de excluirse mutuamente. Este artículo argumenta, desde una perspectiva histórica, que el debate entre la psicología y el cerebro en la clasificación psiquiátrica no es nuevo y tiene un aire de déjà vu. Las primeras clasificaciones del siglo XVIII (de Boissier de Sauvages) basadas en la taxonomía científica debían describir las enfermedades tal cual existían en la naturaleza. Emil Kraepelin asoció con éxito la psicopatología y la investigación del cerebro, anticipando la interacción entre DSM y RDoC. Los síntomas del DSM siguen siendo valiosos porque son los únicos datos que se pueden observar de forma inmediata y directa. La ciencia computacional es un instrumento prometedor para interconectar, en el futuro, datos psicopatológicos y neurocientíficos.

Psychopathologie et neurosciences peuvent-elles coexister dans les classifications psychiatriques ?

Une crise de confiance a été déclenchée par la déception que la validité diagnostique, un objectif important, n'ait pas été atteinte avec la publication du DSM 5. Le projet des critères de domaines de recherche (RDoC), qui fournit un cadre pour la recherche neuroscientifique, a d'abord été conçu comme une alternative au DSM. Cependant, le RDoC et le DSM sont complémentaires plutôt que mutuellement exclusifs. D'un point de vue historique, cet article soutient que le débat opposant la psychologie et le cerveau dans la classification psychiatrique n'est pas nouveau et a un air de déjà-vu. Nous revenons aux premières classifications fondées sur une taxonomie scientifique à la fin du XVIIIe siècle avec Boissier de Sauvages, qui étaient censées décrire les maladies, telles qu'elles existaient réellement dans la nature. Emil Kraepelin a associé avec succès la psychopathologie et la recherche sur le cerveau, préfigurant l'interaction entre le DSM et le RDoC. Les symptômes du DSM restent valables parce qu'ils sont les seules données qui sont immédiatement et directement observables. La science computationnelle est un instrument prometteur pour interconnecter les données psychopathologiques et neuroscientifiques à l'avenir.