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Conflict of Interest in Neuropsychopharmacology: Marketing vs. Education

Thomas A. Ban

THOMAS A. BAN: RDoC IN HISTORICAL PERSPECTIVE
Redefining Mental Illness by Tanya M. Luhrmann. Samuel Gershon's qestion

Collated Document
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This collated document includes Thomas A. Ban's essay, "RDoC in Historical Perspective," posted on February 19, 2015, and includes a critical question by Samuel Gershon regarding the RDoC and the other exchanges that followed the posting of this essay.

Six participants exchanged a total of nine postings, including three postings by Samuel Gershom (of which one was incorporated in Ban's essay), two postings by Thomas A. Ban, and one posting each by Bernard Carroll, Jose de Leon, Martin M. Katz and Antonio Nardi. The last entry in this exchange was made on October 1, 2015.

This collated document is now open to all INHN members for final comment.

Thomas Ban	February 19, 2015	essay
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RDoC IN HISTORICAL PERSPECTIVE
Redefining Mental Illness by Tanya M. Luhrmann. Samuel Gershon's qestion

Thomas A. Ban

*In her article, "Redefining Mental Illness", published in the Sunday Review of New York Times on January 17, 2015 (http://www.nytimes.com/2015/01/18/opinion/sunday/t-m-luhrmann-redefining-mental-illness.html?_r=0), **Tanya Luhrmann** wrote that in 2013, Thomas R. Insel, the director of the National Institute of Mental Health (NIMH) of the United States "announced that psychiatric science had failed to find unique biological mechanisms associated with specific diagnoses" and "diagnoses were neither particularly useful nor accurate for understanding the brain, and would no longer be used to guide research". She pointed out that Insel dismissed "a decades-long tradition of diagnosis-driven research" and introduced a program he called Research Domain Criteria in which "all research must begin from a matrix of neuroscientific structures (genes, cells, circuits) that cut across behavioral, cognitive and social domains (acute fear, loss, arousal)". By doing so, Luhrmann asserts, the NIMH, similar to the "British Psychological Association, rejects the centrality of diagnosis", albeit for quite different reasons.*

On January 18, the day after Luhrmann's article was published, **Samuel Gershon** sent an e-mail with the subject **"help me to understand",** to Bernard Carroll and Tom Ban, copied to Roy Chengappa and Gurhjinder Mali that reads: **"The NYT last Sunday, in the Sunday Review section on page 5, has an article entitled 'Redefining Mental Illness' by TM Luhrmann of Stanford which says that NIMH 'jettisoned' a decade long tradition of diagnosis driven research and mandates that all research must begin from a matrix of neuro-scientific structures, such as genes, cells, circuits that cut across behavioural, etc. domain. How can one do this as (A) the diagnostic system is in fact very defective, and (B) the data in the genetic realm is also undefined? What are the benchmarks"?**

Development that lead to the RDoC began in the mid-1950's with expectations that findings on the mode of action of therapeutically effective psychotropic drugs would provide information on the biochemistry of mental diseases to guide development towards rational pharmacological treatments (Wikler, 1957). As the therapeutic effect of the same drug, in the same dose, in patients with the same diagnosis was inconsistent, Fritz Freyhan (1959), a German born American pioneer of psychopharmacology suggested a pharmacological re-evaluation of

diagnostic concepts in psychiatry. This did not happen. Instead, a statistical methodology, the randomized clinical trial (RCT), was adopted for the demonstration of therapeutic efficacy of psychotropic drugs in pharmacologically heterogeneous diagnostic populations (Ban 2004, 2011). Simultaneously with this development a newly introduced biochemical technology rendered drug- induced changes in the concentration of neurotransmitter monoamines in the brain accessible to measure (Ban 2006; Bowman, Caulfield and Udenfriend, 1955) and an avant-garde intramural research program at the National Institute of Mental Health of the United States embarked on the study of the biochemistry of mental illness (Bunney and Davis, 1965).

To meet the need of RCTs, rating scales (Guy, 1976) sensitive to document changes and consensus based diagnoses which can reliably identified, as DSM-III diagnoses (American Psychiatric Association 1980; Ban 2000a) were introduced. The replacement of psychopathology by psychiatric rating scale scores, and psychiatric nosology derived diagnoses (nosological entities) by consensus-based diagnostic algorithms profoundly affected psychiatry by confounding developmental anomalies (abnormal psychology) with psychopathology (Jaspers, 1910) and extending the scope of psychiatry from pathologies in mental processing to behavioral anomalies with compromised social functioning. By the end of the 1980s, psychopathology (Jaspers, 1913) and psychiatric nosology (Ban, 2000b), the disciplines which enabled psychiatry to detect the differences in the pathologies in the processing of signals in the brain and in the organization of these pathologies in time, were forgotten languages in psychiatry (Ban, 2013).

By the early 1990s, it was evident that the pharmacological heterogeneity within psychiatric diagnoses prevented the generation of valid information on the biochemistry of psychiatric diseases, blocked the development of rational pharmacological treatments and interfered with the optimal use of psychotropic drugs (Ban 1969, 1987, 2004). Yet, when the recognition that the primary targets of psychotropic drugs are encoded by genes which are identified ushered in a molecular genetic era in neuropsychopharmacology, the story of the neurotransmitter era was replicated. Since the pharmacological heterogeneity, now within the broad consensus-based diagnoses was not resolved, similar to findings in biochemical studies in mental illness, findings in molecular genetic studies, remained inconsistent, the results of one study could not be replicated in others (Ban, 2002).

This was the state of affairs in 2010 when the RDoC was launched by Bruce Cuthbert and Thomas Insel, NIMH's Director (Cuthbert and Insel, 2010 a, b; Insel et al., 2010). The objective of the RDoC is to develop end points for psychiatric research based on the biological substrate involved in the shaping of mental activity and/or altered in abnormal mental activity. To achieve this objective "fundamental domains" of "behavioral functioning" are related to their underlying neurobiology by the identification of the "sites of dysregulation" that becomes manifest as "psychosis" on "neurobiological circuit maps" (Cuthbert, 2010a, b; Insel and Cuthbert, 2009). Thus, in the RDoC, the three "psychic structures" of Carl Wernicke (1881, 1899, 1900), the afferent "psychosensory," central "intrapsychic" and efferent "psychomotor," based on Griesinger's (1843) "psychic reflex", is replaced by five "domains" of "neurobiological circuits," labeled as "negative affect," "positive affect," "cognition," "social processes" and "arousal/regulatory system"; psychopathological symptoms by "circuit-based constructs," such as "fear," "distress," "aggression," etc.; and diagnostic end points (nosological hypotheses), by positions in "neurobiological circuit-based matrices" in which the rows consist of "circuit-based constructs" and the columns which determine "circuit-based units" by "genes," "molecules," "cells," etc.

In a historical perspective, the RDoC is a tabula rasa, in which 200 years of development in "psychiatry" is summarily dismissed. As presented, it is floating in the air, without any anchor in clinical reality. But would the population of "circuit-based units" defined by "nosological homotyping" (Ban, 2008), using a matrix in which the rows consist of psychopathological symptoms, and the columns which determine "nosological homotypes" by nosological organizing principles, such as form of onset, course, polarity and outcome (Ban, 2000b; Kraepelin, 1910; Leonhard, 1957), the RDoC could provide a bridge between past and future psychiatry (Ban, 1989; Ban and Ucha Udabe, 1995). "Nosological homotypes" are the most homogeneous populations in terms of psychopathology and psychiatric nosology and if Jacques Moreau de Tours (1845) contention that patients with different mental pathology respond differently to the same drug, "nosological homotypes" provide a suitable population for psychiatric and neuropsychopharmacological research.

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February 19, 2015

Bernard Carroll's reply to Samuel Gershon's question

I thought the Luhrmann piece was just pretentious pabulum and from an anthropologist, yet! Your reference to NIMH concerns RDoC - a contrived matrix of metaphysical constructs developed by armchair bound, top-down bureaucrats with too much time on their hands - I'm talking about Insel and his lieutenant Cuthbert. Dr. Insel doesn't seem to understand the need to advance nosology by incorporating biomarkers along with clinical symptoms in diagnostic definitions, as happened in general medicine. Consider where we would end up if, for instance, we lumped Cushing disease together with juvenile onset diabetes mellitus, Type II diabetes mellitus, severe psychological or physiological stress, metabolic syndrome, anorexia nervosa, and pregnancy on the basis of an abnormal glucose tolerance test, which these all can display. We can expect that eventually the RDoC matrix that Dr. Insel insists should be adopted in new grant proposals will go the way of the eccentrics and epicycles of 16th Century astronomy. The pressing issue is how much damage will be done before that happens?

March 5, 2015

Thomas A. Ban's comment on Bernard Carroll's reply to Samuel Gershon's question

I share Dr. Carroll's concern about the adequacy of lumping together people who share one or another biological property for deriving clinically meaningful populations in psychiatry, as done in the RDoC. I also share his view about the desirability of having biological markers of psychiatric disease. Yet, I wonder whether it is realistic to look for such markers as he suggests, before the identification of the lithium responsive subpopulation within the bipolar disorders, the chlorpromazine responsive subpopulation within the schizophrenias or imipramine responsive subpopulation within the depressions.

October 1, 2015

Samuel Gershon's response to Bernard Carroll's answer

I agree with you. And if I want to write a grant on bipolar disorder, they tell me not to start with the diagnosis of bipolar disorder, but start with the basis of it: genes, microcellular biochemistry and neural circuits. Very good. But I don't know which they are nor does anyone else. So how do I or anyone else write a grant? I know, you make up a new language! At Pittsburgh I was invited by my good friend the professor of the philosophy of science to his major and important lecture. I did not understand one word, but I presume the main audience did. Therefore, these philosophers can only talk and be understood by other philosophers. Sounds very unscientific. Let us try and keep each other sane".

March 12, 2015

Martin M. Katz's comment

The Research Domain Criteria (RDoC) p rogram recalls an earlier time, the early 1970's, when the NIMH sought to launch an ambitious collaborative program on the psychobiology of depression, designed primarily to test the then new hypotheses identifying the role of dysfunction in central neurotransmitter systems. In view of the variations in the diagnostic systems applied at that time, and the resultant ambiguities in language, a diagnostic system applicable for research was required that would be more reliable and generalizable across studies. To render the then controversial and unreliable diagnostic system suitable for research, a group led by Eli Robins, Robert Spitzer and Jean Endicott, was convened by the NIMH's Clinical Research Branch to refine the definitions so that reliable operational criteria could be articulated for each of the categorical diagnostic types. This contracted effort resulted in the "research diagnostic criteria", the RDC, published by Spitzer et al (1979). In addition, a data collection instrument was

constructed that would ensure that all domains and criteria of psychopathology would be covered in the diagnostic interview, the "schedule for affective disorders and schizophrenia", the SADS (Endicott and Spitzer, 1989).

The RDC provided the structure for the then developed DSM III, an empirically derived, presumably, atheoretical system, designed to be more reliable than previous systems applied in psychiatry. Spitzer, a developer of the RDC was selected to serve as Chairman of the Classification Committee that then created the DSM III. In today's view the RDC could be construed as a more elementary version of the currently proposed RDoC, and thus, a precursor of the RDoC It relied on traditionally accepted symptoms, then articulated them more explicitly, thus, increasing their reliability as elements to be utilized in the structure of the system.

The field was not yet ready to define the underlying mechanisms of the disorder or drug actions in terms of dysfunction in neurochemistry or associated neural circuits or genetic bases. Applying the RDC to research on the psychobiology of depression as conducted in the collaborative (Maas et al., 1980) and other programs during this period, permitted significant advances in the science and in psychopharmacology, assisting in identifying relationships between the neurochemistry underlying the diagnoses and the behavioral elements that contributed to the symptomatology of the categorical disorders.

Nevertheless, as Maas and I pointed out (1994), the diagnostic system fell short of advancing the science beyond a certain point, and could in fact, be an obstacle in attempting to uncover the neurobehavioral mechanisms underlying the disorders and the bases for the efficacy of the established antidepressant agents. We contended then, that the components or dimensions that structured the disorder, along with the effects on central neurotransmitter systems, should be the starting points for these types of investigation and not the more complex, still partially understood diagnostic types. We demonstrated how that substitution worked in Katz et al 1994, a study that linked drug-induced changes in metabolites of serotonin and norepinephrine with different changes in components of behavior and mood, e.g., 5-HIAA with changes in anxiety, MHPG with motor activity. Again, I see these earlier findings now as further evidence that relying on diagnosis as we knew it then, as central to uncovering basic information about the disorders or their reactivity to chemical agents that impact central neurotransmitter systems, was the "wrong" path, incapable of resolving problems in this realm of research. We proposed at the time to set diagnosis aside, to adopt in its place a componential or dimensional approach to

defining psychopathology, in order to advance science in this area. In that case, based on an intensive analysis of a large multisite patient sample, we identified as major dimensions for depression, depressed mood-retardation, anxiety –agitation-somatization, and hostility, with additional components from disturbances in motor activity and cognitive impairment. Today the Insel-Cuthbert RDoC approach leads to a somewhat similar structure on the behavioral side, but looks much beyond the neurochemical framework we applied in the 1970's and '80's. They have included more recent work on neural circuitry and genetics and provided space for expected further advances in these areas.

Their proposal and the target they are working towards in the matrix is a bold attempt to provide a set of long term goals, a structure to guide future research, while releasing the field from its decades-long reliance on an inapplicable diagnostic network. I admire the effort and with them, believe that it is the proper direction and further, that theirs is a well thought out plan to achieve its aims.

Achieving their goal of completing the matrix is, however, a work in progress and the long term goals still well beyond their grasp. The pressing question we face today relates to investigations in the here and now. How do investigators deal with the traditional centrality of diagnosis in clinical research, generally, and in clinical trials, specifically, in the interim, i.e., in the meantime, while we await the long term goals of the RDoC to be achieved?

My recommendation is straightforward. It is that the RDoC program continue as it has, to integrate current advances in neurochemistry, molecular biology, neural circuitry, genetics into the matrix columns. To effect associations with clinical phenomena, with psychopathology the program needs, however, to take another path. Why not adopt the dimensions, the componential approach that have already been developed as the central clinical phenomena, those

The facets that are currently capable, as evidenced in psychometric research, of being measured validly. As one example, I refer to the system that my colleagues and I developed and is now well represented in several publications (Katz et al., 1984, 1994, 2004; Katz, 2013). These studies identifying well-established reliable, quantitative dimensions, have already been applied in several areas of clinical research, specifically, in the creation of a new, componential model for the clinical trial of putative antidepressants. This system based on these earlier studies can be productively applied to a range of new work in these areas and serve well in this field while we await further progress of the RDoC program.

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March 19, 2015

Antonio E. Nardi's comment

I read with great enthusiasm your essay on RDoC in Historical Perspective, posted in Perspective on INHN's website on the 15th of February, 2015. Some of my colleagues and I

published in 2013 (Nardi et al., 2013) discussing the difficulties of psychiatric diagnosis and the different points of view nowadays concerning RDoC and DSM-5.

I would like to highlight some ideas presented in that Editorial. For instance, we pointed out that diagnosis in psychiatry has never been an easy task. Every psychiatrist or researcher struggles with diagnostic limitations on a daily basis. The mixture of symptoms, behavior, culture, prejudice and science has always been the subject of the most enthusiastic debate, but with very few results. The release of the Research Diagnostic Criteria (RDC, Feighner et al., 1972), soon followed by the DSM-III, and their diagnostic criteria, brought greater reliability to psychiatric diagnosis, but yielded almost no gains in validity. Many changes for better and for worse were implemented in the subsequent editions of the DSMs. In 2013, the latest edition – DSM-5 - was published. Even though we may criticize some of its aspects and support others, the great development observed in clinical research after the third and fourth editions of the DSM cannot be denied. The main principle of all versions of the DSM is that they are important tools for research and legal work. For clinicians, they serve as guidelines only, and should be no more than that. Clinical practice is an art in which we have to mix science and different levels of philosophy.

Thomas Insel (2013), director of the National Institute for Mental Health (NIMH), published an editorial stating that the greatest provider of funds for mental health research will not accept the DSM-5 as a valid tool for research. This statement creates an uncomfortable situation for the American Psychiatric Association, when the DSM-5 is being presented to the world as the basis for the most modern and reliable diagnoses.

We have the firm point of view that the DSM-5 categories are not supposed to be a perpetual “gold standard.” First, they represent a set of contemporary criteria for an accurate diagnosis that can and will change in the next edition of the manual. Second, the use of DSM-5 does not weaken the Research Domain Criteria (RDoC) project. In fact, the two publications could work together and mutually support each other. Any diagnostic system should be based on emerging research data, but symptom-based categories are what we currently have. We certainly agree with Insel in that research needs to gather genetic, imaging, physiologic, and cognitive evidence in order to improve our understanding of how all biological data - rather than

symptoms alone - cluster and how these clusters relate to treatment response. We can already identify some of these issues in the DSM-5. Some new categories may not be sufficiently sound from the scientific point of view. For example, mild neurocognitive disorder, binge eating disorder, and disruptive mood dysregulation disorder are all very close to normal behavior, and we still lack clear cut-off points to improve diagnostic reliability. Some other categories had their formerly strict criteria changed to more open possibilities, and that should be taken very carefully by clinical and research colleagues. No diagnostic classification will address all human needs in this regard, and it must be borne in mind that not all problems in life are caused by mental disorders.

NIMH might orient its research away from DSM categories. According to Insel, patients with mental disorders deserve better. But what could be better than DSM-5 at present? Insel's editorial informs that the NIMH has released the RDoC “to transform diagnosis by incorporating genetics, imaging, cognitive science, and other levels of information to lay the foundation for a new classification system.” The NIMH tried to create a new nosology based on five major systems: 1) negative valence systems; 2) positive valence systems; 3) cognitive systems; 4) systems for social processes; and 5) arousal/modulatory systems. Even though Insel declared that at present we cannot design a system that is based on biomarkers or cognitive performance because we lack the data, symptoms and long-term follow-up is what physicians have available in practice today to support diagnosis. The data required for a precise diagnosis - one that we can really trust - will come in the future, but the patient is suffering now.

The RDoC project is a research framework, not a clinical tool. It is a decade-long project leading perhaps to a better psychiatry, with better diagnosis validity. Working with psychiatric diagnosis means dealing with and searching for all the possibilities to improve future classifications. The RDoC and the DSM are not opposing each each other; they are different pathways by which psychiatry can move to improve diagnosis. Research should be our priority in obtaining data, as research data ultimately, will be the basis to helping people with mental disorders. Physicians should be aware of the limitations of our classifications, but also that they are the best we have at the moment. As for the future, we need robust research data and less fear of challenging psychiatric diagnosis.

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2. Feighner JP, Robins E, Guze SB, Woodruff RA, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry1972; 26: 57-63.

3. Insel T. National Institute of Mental Health: Director's Blog [Internet]. Transforming diagnosis. 2013 Apr 29

March 26, 2015

Samuel Gershon's reply to Martin M. Katz and Antonio E. Nardi's comment

I agree with Marty Katz and Antonio Nardia that the etiology of mental disorders is not understood or adequately explained scientifically by any system discussed. Further, we do not have a range of pharmacotherapeutic agents that specifically and effectively treat any of our psychiatric disorders and the introduction of very many psychiatric medications has not contributed meaningfully to any of these questions. The situation of psychodynamic explanations and therapies has led us no further. Also, non- dynamic psychotherapies have a weak basis for efficacy in major psychiatric disorders. Yet oddly, the oldest therapeutic pharmacotherapeutic agent, Lithium, has been with us since its reintroduction for 65 years. During this period, we have defined its therapeutic profile and recently, Duffy and Grof have helped further in this definition by defining a group of manic-depressive patients that are responders vs. a group of non-responders and describing a genetic linkage in the responders. Thus, all possible techniques of looking and learning can contribute to the answer.

Reference:

Duffy A, Horrocks J, Doucette S, Keown-Stoneman Ch, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. The British Journal of Psychiatry 2014; 204: 122-8.

May 21, 2015

Jose de Leon's comment

Thomas A. Ban started his commentary on the RDoC by referring to an article published by Luhrmann, an anthropologist, on January 17, 2015, in the *New York Times* (*NYT*) that did not reflect favorably on contemporary psychiatric nosology (*http://www.nytimes.com/2015/01/18/opinion/sunday/t-m-luhrmann-redefining-mental-illness.html?_r=0).* This time, the *NYT* comment was published without any reply from a psychiatrist. Jeffrey Lieberman, past president of the American Psychiatric Association (APA) and chairman of an academic department in New York, had to ventilate his frustration in Medscape (http://www.nytimes.com/2015/01/18/opinion/sunday/t-m-luhrmann-redefining-mental-illness.html?_r=0). The attentive reader will observe that I used the words "this time". I personally believe the *NYT* has been presenting a progressively worse view of psychiatric nosology since the spring of 2013 when the *DSM-5* was published. I suspect that any objective observer would agree that psychiatry's prestige as a scientific enterprise has coursed downhill for the past two years.

In my view the anthropologist's article in the *NYT* was the third step in this downhill process. This course started with a comment on April 29, 2013, by Thomas Insel, Director of the National Institute of Mental Health (NIMH), who explained just before the *DSM-5*'s official publication in May 2013 that it lacked "validity" (http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml). Not surprisingly, May 7, 2013, brought a comment in the *NYT* titled "Psychiatry's guide is out of touch with science, experts say (http://www.nytimes.com/2013/05/07/health/psychiatrys-new-guide-falls-short-experts-say.html?pagewanted=all&_r=0). To try to address that marketing catastrophe, Insel and Lieberman published an online article together (http://www.nimh.nih.gov/news/science-news/2013/dsm-5-and-rdoc-shared-interests.shtml).

The second step was the *NYT* column entitled "Heroes of Uncertainty" by David Brooks, a political columnist, which appeared on May 29, 2013 (http://www.nytimes.com/2013/05/28/opinion/brooks-heroes-of-uncertainty.html?_r=0). I am surely biased as I earn my salary by treating the most difficult psychiatric patients in the public system of a state with 4 million people, but I thought the description in "Heroes of Uncertainty"

fairly accurately describes[1] what I do for a living and is a pretty good depiction of what many excellent psychiatrists do every day in my state's public system. I consult with these psychiatrists, who work with limited time, resources and access to medical records, but are able to treat very difficult patients. This time Lieberman was given the opportunity for a brief rebuttal to Brooks by the *NYT* (http://www.nytimes.com/2013/05/30/opinion/psychiatry-on-the-scientific-spectrum.html?r&_r=0). Moreover, he expanded his view in the APA newspaper *Psychiatric News* on July 1, 2013, with an article titled "Psychiatry: Nothing to Be Defensive About" (http://psychnews.psychiatryonline.org/doi/abs/10.1176/appi.pn.2013.7b19) One of Liebermann's major concerns was that Brooks questioned the scientific status of psychiatry. Brooks stated, "The recent editions of this manual exude an impressive aura of scientific authority…The problem is that the behavioral sciences like psychiatry are not really sciences; they are semi-sciences." Since Brooks is not an expert in scientific methodology, his definition of psychiatry as a "semi-science" does not appear "scandalous" to me; my view on the application of scientific methodology to medicine and science has previously been described in detail.[1] Following Paul McHugh,[2] I believe that psychiatry is 150 years behind medicine and, following Karl Jaspers,[3] I think that psychiatry is a hybrid discipline combining the methodology of the natural sciences (explaining) and of the social sciences (understanding). In my opinion, psychiatry is not only neurology and not only abnormal psychology[4] since it includes disorders that can be called "neurological" and follow the medical model (e.g., Alzheimer disease) and also the psychological abnormalities that McHugh[5] describes in three of his four perspectives in psychiatry, namely "behaviors", "dimensions" and "self and life story". His fourth perspective is "disease", which applies to Alzheimer disease.[4] Supported by the wisdom of Jaspers and McHugh, I feel comfortable disagreeing with Lieberman about the "scientific" status of contemporary US psychiatry. Moreover, from the practical point of view, I believe that US psychiatry has to be "defensive" about many things. I titled an editorial in a psychopharmacological journal "Paradoxes of US Psychopharmacology Practice in 2013: Undertreatment of Severe Mental Illness and Overtreatment of Minor Psychiatric Problems."[6]

Like Ban, I am a European psychiatrist transplanted to North America; therefore, my views on the interaction between psychiatry and psychopharmacology are very similar to his, and I consider his approach of using clinical symptoms[7-9] to be one of the main ways that psychiatry can move forward with the "fantasy" of personalizing psychiatric treatments.[10] To criticize the

RDoC, Ban uses a historical approach going back 150 years to Griesinger, while my historical approach[11] looks back only 100 years by proposing that Jaspers's words for Wernicke's approach, "brain mythology", apply to the RDoC, as well. The RDoC appear to forget that some of the so-called disorders of the *DSM-5* have no clear boundaries with normal human behavior, and can simply be defined as "abnormal psychology"; these disorders do not follow the medical model which was the "ideal" of Kraepelin[12] and the US neo-Kraepelinians.[13] In summary, I do not have Ban's wisdom, but I cannot find any statement in his comment with which I can disagree.

I started to admire Carroll and Gershon 30 years ago, during my psychiatric training; therefore, I am not sure I can do a good job of critiquing them. Moreover, I totally agree with them that the RDoC are an absolute catastrophe for research in severe mental illness, including schizophrenia, bipolar disorder and severe depression. To conclude, Kraepelin,[14] 100 years ago, tried to save psychiatric nosology by developing a Research Institute using the neurosciences of his time; he failed but at least he had a thorough understanding of clinical and historical issues in psychiatry during his time,[15] while the NIMH leaders do not appear to have mastered clinical issues and have no historical knowledge. They combine Kraepelin's marketing of curing mental illness[16] with Wernicke's "brain mythology". It appears that they have not read the Harvard philosopher George Santayana, "Those who cannot remember the past are condemned to repeat it."[17]

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