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COMMENTARY

Classification issues in women's mental health: clinical utility and etiological mechanisms

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It is now well known that significant anatomical and functional differences exist between male and female brains (e.g., Becker et al. 2007). Many sex differences with respect to mental disorders also have long been noted. For example, compared to men, women show overall higher rates of mood and anxiety disorders; a later onset of illness for the severe and persistent disorders of schizophrenia and bipolar disorder, but no difference in overall prevalence; more rapid cycling in bipolar disorder; and lower overall rates of substance abuse but faster escalation to addiction (Becker and Hu 2008). For the most part, however, these differences have been considered in terms of such parametric aspects as age of onset, severity, and course, rather than any fundamental differences in the nature of the psychopathology or pathophysiology.

A major exception to this view has come from disorders, or features of disorders, that are unique to women—those related to the menstrual cycle, pregnancy and childbirth, and the menopause. Psychopathology related to these conditions can be reasonably imputed to the hormonal and related changes that accompany these major transition points in a woman's life. Strong evidence exists for the onset or exacerbation of disorders with respect to these time points. However, optimal ways to conceptualize and diagnose disorders that are coincident with or follow these changes remain to be determined.

The 14 papers appearing in this issue of the journal comprise a comprehensive cross-section of expert opinion regarding potential changes to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V and International Classification of Diseases (ICD)-11 revisions with respect to mental disorders that uniquely affect women. The articles address extremely important areas that are critical to the health of women, their children, and other family members. Written by investigators working in a wide variety of specific application areas, the suggestions in this section will no doubt contribute substantially to deliberations of the relevant DSM-V and ICD-11 revision committees. These include such critical topics as whether major mental disorders of the peri- and postpartum period—notably, puerperal psychosis and depression—should be considered as separate entries in their own right or included as specifiers to currently defined disorders; whether premenstrual dysphoric disorder should be moved from its current position in the appendix to the main section, and if so, where; and whether conditions not yet defined, such as post-traumatic stress disorder due to childbirth and prolonged grieving, would add value if included in the DSM/ICD. Another important aspect concerns the time frames for the various conditions—both in terms of pre- vs. postbirth onset, and the time window after birth for such syndromes as postpartum depression and puerperal psychosis. Finally, there are also important implications for treatment; one notable exemplar, mentioned by multiple authors, is that estrogen may be a viable treatment for depression in the perimenopause but not for postmenopause.

The outcomes of the discussion on these points have important clinical significance. The issues include encouraging clinicians to attend to symptoms at various points during pregnancy or after birth, or menstrual phases that might otherwise be overlooked or wrongly diagnosed; to permit insurance coverage for important sources of distress and impairment; to provide guides for treatment; and to furnish information about history and course of illness for

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future health providers. As various authors elaborate, further research may help establish the utility of these various improvements, as they are instantiated in formal diagnostic systems. There is thus undoubted clinical significance in refining the criteria for these serious disorders, and the results should lead to better management of these severe disorders of women's health.

In a longer-term perspective, we need to discover fundamental new knowledge about the brain and behavior that leads to new and better treatments—and ultimately effective preventive interventions—for all mental disorders, including gender-specific conditions. Such a goal is particularly germane for the National Institute of Mental Health (NIMH), charged with reducing the burden of suffering from mental disorders through funding innovative research. From this viewpoint, the papers in this section implicitly attest to the insufficient knowledge base regarding the fundamental etiology of mental illness.

A good illustration of this point is provided by the literature on postpuerperal psychosis. While this syndrome appears to resemble bipolar disorder with respect to long-term course, the precise degree of resemblance to "typical" bipolar disorder is uncertain (as is the cause of episode onsets linked to the postpartum period). However, this comparison begs two important questions: What is the pathophysiology of bipolar disorder? What is the relevant circuitry for mood regulation? In spite of all the clinical science of the past several decades, we still possess only a rudimentary idea of exactly what goes wrong in brain systems to eventuate in the classic presentations of bipolar disorder. Given this lack, how can we specify the ways in which a postpuerperal psychosis actually is related to classical bipolar illness?

Questions such as these arise from the fact that current psychiatric nosologies were developed approximately 30 years ago and necessarily based upon consensus regarding clinical symptom constellations given the lack of knowledge about the structure and functioning of the brain. The classic formulation of Robins and Guze (1970) and subsequent refinements were developed primarily with the aim of increasing reliability in diagnosis, with the assumption that future developments such as laboratory tests and family histories would validate the categories. However, these assumptions have increasingly proved problematic. Co-morbidity among disorders occurs at much higher rates than would be expected by chance, diagnostic categories are increasingly over-specified, and yet "not otherwise specified" diagnoses are very common. Perhaps even more troubling for modern science, the categories do not reflect the burgeoning knowledge base about genetics, neural circuits, and behavior relevant to mental disorders.

Given these problems, NIMH included as Strategy 1.4 of its new Strategic Plan the following aim: "Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" (National Institute of Mental Health 2008). This aim is being implemented with a new initiative termed the Research Domain Criteria (RDoC) project. Essentially, the goal is to create a neuroscience-based framework for studying mental disorders based on the rapidly accelerating growth of basic knowledge about genes, the brain, and behavior. Translating such knowledge to mental disorders requires a selection of subjects based on basic functional dimensions of behavioral neuroscience, rather than on heterogeneous clinical symptoms. Identifying and delineating such basic dimensions will comprise the major part of the RDoC process, and an NIMH project group, in conjunction with external advisors, has been developing a work plan and initial framework.

The classification system is to be developed in stages over a 2- to 3-year period. Fear circuitry and executive functioning are examples of two functional domains where the relevant circuitry and behaviors seem relatively clear, and these have been selected as the initial areas to be developed; other examples might include reward circuitry and frontostriatal circuits. Ultimately, the specification for each area will consist of a set of variables at different levels of analysis, such as genes, molecular/cellular mechanisms, behavior, and clinical measures. Importantly, investigators can select measures from any of these levels as the independent variable for grouping patient samples rather than being constrained to symptom-defined diagnostic categories; further, independent variables may be dimensional rather than binary (disorder present/absent). Thus, patient subjects with relevant presenting psychopathology (e.g., all patients presenting for treatment at an anxiety disorders clinic) might be grouped on the basis of a genetic polymorphism or a particular response to a neuroimaging task rather than a DSM/ICD diagnosis; in this manner, investigators can query relevant mechanisms as they cut across traditional categories.

A major goal of the RDoC project is to be fully open and transparent. The initial overall framework and draft set of domains will appear on the NIMH web site to permit commentary over several weeks' time. Continuing input will be solicited through conferences on each of the domains, with further opportunities for commentary on the NIMH web site. The final specifications for each domain will be posted on the NIMH site for downloading without charge. By definition, a major goal of RDoC is to foster continuing refinements to the various domains through research. Accordingly, an important aspect will be to create a set of criteria by which changes to the domains and/or their specifications can be accomplished on the basis of new empirical findings.

Vis-a-vis women's health, an example of an independent variable with respect to peri- and postpartum disorders

might be to select subjects for particular patterns of neural circuit activation in response to hormonal changes rather than on the basis of particular presenting symptoms. For example, recent work from Berman et al. has demonstrated powerful effects of estrogen on reward circuitry (Dreher et al. 2007). In a broader sense, a better explication of hormonal effects on neural circuits may not only reveal mechanisms of risk for women but can inform our understanding of the relevant disorders more generally. As one example, activation of the prefrontal cortex during a working memory task is dependent on gonadal steroid stimulation, providing a potential approach to one of the fundamental deficits in schizophrenia (Berman et al. 1997; Marx et al. 2009).

It should be clear from the preceding sections that the RDoC initiative will minimally inform the current process of the DSM and ICD revisions. Rather, the goal is to begin the process of developing a classification system for research purposes that can inform future psychiatric nosologies. The RDoC process, by adopting an explicitly translational approach, is intended to foster research that uses information from basic genomic and molecular/cellular research to further our understanding of how cognition and behavior are implemented and constrained. In this manner, it is hoped that the knowledge gained through modern behavioral neuroscience can be successfully translated to new and more effective interventions in women's health as in all areas of mental disorders.

Conflict of interest T. Insel and B. Cuthbert report no biomedical financial interests or potential conflicts of interest.

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