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•Forum•

Challenges to psychiatry's symptom-based diagnostic system

Genetic findings are challenging the symptom-based diagnostic classification system of mental disorders

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Summary: The present diagnostic classification of mental illnesses is primarily based on symptomatology. A recent cross-disorder genome-wide association study revealed that there were genetic similarities between multiple clinically defined diagnoses (including schizophrenia, bipolar disorder, depression, attention deficit hyperactivity disorder, and autism spectrum disorder) on regions of chromosomes 3p21 and 10q24 and single-nucleotide polymorphisms (SNPs) within two L-type voltage-gated calcium channel subunits of *CACNA1C* and *CACNB2*. These findings suggest that the pathogenesis of these five independent disorders are related. Such cross-disorder genetic studies challenge the current symptom-based diagnostic classification of mental disorders. Researchers need to identify creative ways to bridge the gap between these two approaches to understanding and labelling mental disorders.

Keywords: diagnostic classification; cross-disease; genetics

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Mental illnesses are a group of complex conditions that affect populations. The main symptoms include abnormities in perception and cognition that result in behavioral and volitional impairments.[1] Since the work of Kraepelin, mental disorders have been classified into different diseases or disorders based on the pattern of clinical symptoms and the long-term prognosis of the condition. Influenced by this approach to the classification of mental disorders, it has been assumed that clinically distinct phenotypes have different etiologies and, thus, research about the causes and appropriate treatments for mental disorders has been largely confined to disorder-specific silos.[2] The specific etiology of most mental disorders remains unknown, but most scholars working in the field agree that heredity plays an important role in the onset of nearly every type of mental illness and that these hereditary factors often interact with environmental factors during the development and course of mental disorders.[3] Research in genetic epidemiology has shown that many mental illnesses – including schizophrenia, bipolar disorder, depression, attention deficit hyperactivity disorder, and autism spectrum disorder – have high rates of heritability.[4] A recent cross-disorder genome-wide association study found similar genetic sensitivities in these five diagnostically distinct disorders on regions of chromosomes 3p21 and 10q24 and single-nucleotide polymorphisms (SNPs) within two genes that encode L-type voltage-gated calcium channel subunits, *CACNA1C* and *CACNB2*.[5] The specific SNPs were correlated with the age of onset of various mental illnesses, and polymorphism of the calcium-channel activity gene in the five disorders suggests that this gene is important in the onset of all of these conditions. These findings show that despite being classified as distinct conditions in the current diagnostic nosology, genetic research indicates many similarities in the etiology of the conditions.[6]

Clearly, cross-disorder genetic studies challenge the validity of the current diagnostic classification system for mental disorders. The history of psychiatry has included many research-driven changes in the classification systems for mental disorders. The currently used diagnostic systems are quite comprehensive, but they still primarily depend on symptomology. We lack sufficient information about the biological etiology of these conditions,[7] so, like the 'blind man and the elephant', we classify mental disorders based on the external phenomena we can observe (symptoms) rather on the internal causes of the external phenomena

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(etiology). This approach has serious limitations. For example, when a patient complains of 'abdominal pain', even if doctors can accurately describe the characteristics of the pain (e.g., intermittent versus constant, sharp versus dull, etc.), lab tests and X-rays that identify the cause of the pain are much more important in the diagnosis and clinical management of the condition. In most disciplines within modern medicine, diagnostic systems have moved from a symptom-based nosology to classification systems that consider clinical findings (particularly when screening for a condition) but put relatively more emphasis on laboratory results, often requiring them before making a definitive diagnosis. Psychiatry is currently in a transitional period. To move along the trajectory more quickly, increased research emphasis needs to be placed on identifying the genetic and biological mechanisms underpinning mental disorders, and more discussion and debate is needed to decide how best to use this information to supplement or subclassify clinical diagnoses.[8] At present, the calcium-channel activity gene story is the 'hot' research topic in genetic studies of psychiatric disorders; several studies have confirmed its role in a variety of mental disorders, suggesting that it could be a general biomarker for the onset of a wide range of psychiatric conditions.[9] Further work with this group of genes is needed to determine how best to integrate this important finding from genetics into the diagnostics system for mental disorders.

The unproven implicit assumption that phenotypes map neatly onto genotypes has driven the diagnoses, clinical management, and research of mental disorders for decades. Genetic studies of psychiatric disorders have been carried out over the past 30 years, but up until recently almost all of the research has been diagnostic-specific. However, this type of research has been unable to reach any clear conclusions. For example, based on data collected by the Schizophrenia Research Forum (http://www.schizophreniaforum.org/whatsnew.asp), there were 1727 genetic studies about 1008 different genes among patients with schizophrenia reported before 29 January 2016, but many of the positive results (and findings from meta-analyses) could not be replicated. This failure to replicate diagnostic-specific results and recognition of the high rates of diagnostic comorbidity has recently stimulated an increasing number of cross-disorder genetic studies that have found similar genetic characteristics among individuals who are classified with distinct disorders in the current diagnostic systems. These findings put into question the validity of the existing diagnostic systems.[10] But it will be a long time before the genetic research will be mature enough (or inexpensive enough) to use in clinical practice, so the challenge for researchers, clinicians, and administrators is to determine how best to supplement the current phenomenology-based diagnostic system with the new emerging genetic findings. Moving psychiatry forward and improving our ability to effectively treat our patients requires ongoing attention to resolving this controversy about the best method for classifying mental disorders.

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遗传学研究结果对以症状为基础的精神障碍诊断分类系统的挑战

张晨

概述：现有的精神疾病诊断系统主要是依据症状学来分类的。最近一项跨病种全基因组关联分析研究显示，在临床诊断为精神分裂症、双相障碍、抑郁症、注意缺陷多动障碍以及孤独症谱系障碍等疾病的患者中，染色体 3p21 和 10q24 区域内的基因具有相似性，两条 L-型电压门控钙离子通道亚基基因 CACNA1C 和 CACNB2 的单核苷酸多态性也相似。这些研究结果表明这五种看似独立的疾病其病理机制存在着某种关联。这种跨病种研究对现有以症状为基础的精神疾病诊断分类系统提出了挑战。研究人员需要找出创造性方法，消除这两种不同方法对精神障碍理解、分类间的差异。

关键词：诊断分类；跨病种；遗传学

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References

1. Jeste DV, Palmer BW, Rettew DC, Boardman S. Positive psychiatry: its time has come. *J Clin Psychiatry*. 2015; **76**(6): 675-683. doi: http://dx.doi.org/10.4088/JCP.14nr09599
2. Shorter E. The history of nosology and the rise of the Diagnostic and Statistical Manual of Mental Disorders. *Dialogues Clin Neurosci*. 2015; **17**(1): 59-67

3. Zhang C, Lu W, Wang Z, Ni J, Zhang J, Tang W, Fang Y. A comprehensive analysis of NDST3 for schizophrenia and bipolar disorder in Han Chinese. *Transl Psychiatry*. 2016; **6**: e701. doi: http://dx.doi.org/10.1038/tp.2015.199
4. Moreno-De-Luca A, Myers SM, Challman TD, Moreno-De-Luca D, Evans DW, Ledbetter DH. Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. *Lancet Neurol*. 2013; **12**(4): 406-414. doi: http://dx.doi.org/10.1016/S1474-4422(13)70011-5
5. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet*. 2013; **381**(9875): 1371-1379. doi: http://dx.doi.org/10.1016/S0140-6736(12)62129-1
6. Wood H. Neuropsychiatric disorders: Blurring diagnostic boundaries: common genetic risk variants in major psychiatric disorders. *Nat Rev Neurol*. 2013; **9**(4): 181. doi: http://dx.doi.org/10.1038/nrneurol.2013.54
7. Modai S, Shomron N. Molecular risk factors for schizophrenia. *Trends Mol Med*. 2016; **22**(3): 242–253. doi: http://dx.doi.org/10.1016/j.molmed.2016.01.006
8. Cao M, Wang Z, He Y. Connectomics in psychiatric research: advances and applications. *Neuropsychiatr Dis Treat*. 2015; **11**: 2801-2810. doi: http://dx.doi.org/10.2147/NDT.S63470
9. Heyes S, Pratt WS, Rees E, Dahimene S, Ferron L, Owen MJ, Dolphin AC. Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. *Prog Neurobiol*. 2015; **134**: 36-54. doi: http://dx.doi.org/10.1016/j.pneurobio.2015.09.002
10. Gonzalez-Mantilla AJ, Moreno-De-Luca A, Ledbetter DH, Martin CL. A cross-disorder method to identify novel candidate genes for developmental brain disorders. *JAMA Psychiatry*. 2016; **73**(1): published online. doi: http://dx.doi.org/10.1001/jamapsychiatry.2015.2692

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