Neurosci. Bull. June, 2017, 33(3):351–353
DOI 10.1007/s12264-017-0108-3

www.neurosci.cn
www.springer.com/12264

RESEARCH HIGHLIGHT

Biological Subtypes Bridge Diagnoses and Biomarkers: A Novel Research Track for Mental Disorders

Ming Song[1,2] · Zhengyi Yang[2] · Jing Sui[1,2,5] · Tianzi Jiang[1,2,3,4,5]

Received: 30 December 2016 / Accepted: 24 January 2017 / Published online: 21 February 2017

Neuroimaging has shown promise for diagnosing depression, but these diagnostic systems have not performed as well when tested in large multi-site datasets. Recently, a paper published in Nature Medicine [1] has made major progress and provided good cues about how to understand mental disorders, not limited to depression.

It is well known that mental disorders are associated with numerous personal and societal costs. According to the most recent global burden of disease study, mental disorders and substance-use disorders are a leading source of years lived with disability [2]. The World Health Organization estimates that there are >800,000 suicides each year globally, a great many of which are a consequence of a mental disorder. To date, diagnosis in psychiatry, including that of depression, remains restricted to subjective symptoms. Although there is increasing debate about whether to incorporate the concepts of modern biology, especially contemporary genetics and neuroscience, into the diagnosis of mental disorders, current clinical practice is still based on clinical observation, including the identification of symptoms that tend to cluster, the timing of appearance of symptoms, and their tendency to resolve, recur, or become chronic [3]. The regular research paradigm is shown in Fig. 1(A). After all, the differences in genomic variants and brain circuits/networks in studies of people with mental disorders require further validation. One of the critical tests is how well new molecular and neurobiological parameters predict the prognosis or response to treatment. Unfortunately, these parameters, at least for most of the genetic and neuroimaging studies, have fallen short of biomarker standards.

Recent studies suggest one important aspect of the reasons for these challenges [4]. Specifically, the diagnostic heterogeneity in psychiatry might emerge as a major obstacle. According to current clinical thinking, a mental disorder is a psychological syndrome. In fact, a cluster of symptoms can result from different biological processes. For example, depression is a heterogeneous clinical syndrome that is diagnosed when a patient reports at least five of nine symptoms. This allows for several hundred unique combinations of changes in mood, appetite, sleep, energy, cognition, and motor activity. The association between clinical symptoms and the underlying biological substrates is inconsistent and variable at the individual level, even when the diagnosis is depression. On the other hand, there are multiple examples of distinct disorders with remarkably similar clinical presentations, but the pathologies and treatments are entirely different. For example, cough and fever can result from bacterial, viral, or fungal infections, or from autoimmunity, with very different treatments and outcomes. Therefore, it is increasingly necessary to deconstruct current psychiatric groups into biologically

✉ Tianzi Jiang
jiangtz@nlpr.ia.ac.cn

1 Brainnetome Center, Institute of Automation, The Chinese Academy of Sciences, Beijing 100190, China

2 National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China

3 Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia

4 Key Laboratory for Neuroinformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China

5 CAS Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai 200031, China

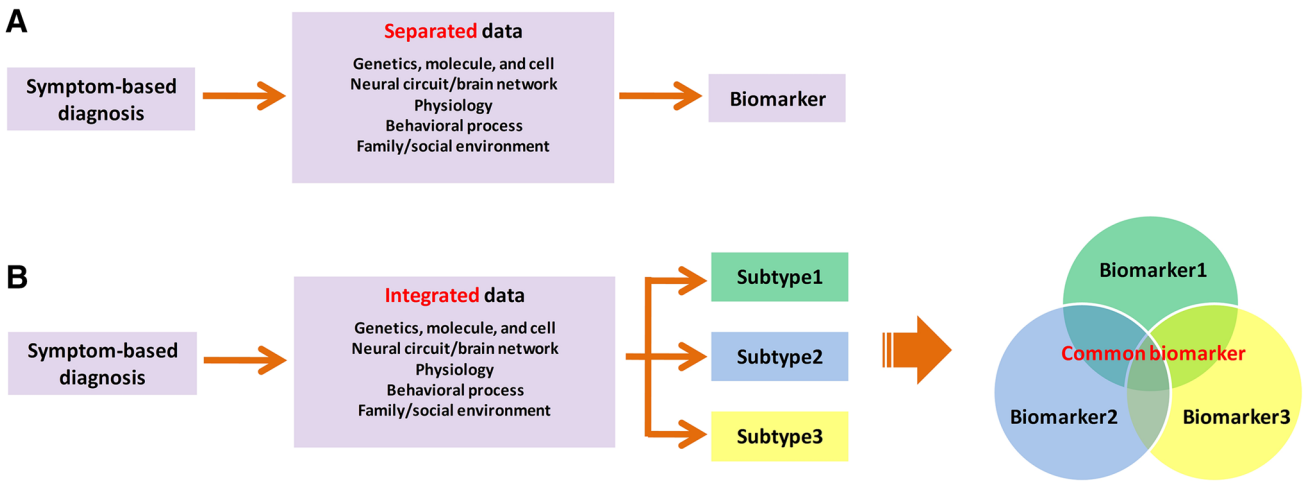

Fig. 1 The regular (A) and novel (B) research tracks for mental disorders

validated subgroups, that is "subtypes", to understand the various aspects of dysfunction associated with disorders and improve the accuracy with which patients are categorized and treated. This was the motivation to suggest in this highlight that biological subtypes should bridge diagnoses and biomarkers, as shown in Fig. 1(B).

So far, there is no consensus about how to derive psychiatric subtypes. Preliminary studies have provided proof-of-concept that different levels of data from the genetic, molecular, and cellular levels, proceeding to the neural circuit level, and on to the level of the individual, family environment, and social context should be integrated to sort individuals with mental disorders into subgroups that are neurobiologically distinct and appear to be biologically meaningful. This probably seems a bit abstract right now, but some studies have provided suggestive starting points. For instance, imaging and neurophysiology have demonstrated three subtypes of attention deficit hyperactivity disorder with significantly different responses to medication [5]. A panel of neuropsychological and physiological measures identified three biotypes that did not respect the clinical diagnosis (schizophrenia, schizoaffective disorder, and bipolar disorder) but were well-validated by external measures (social functioning, brain imaging, and family information) [6]. Notably, a very interesting study by Drysdale *et al.* [1] has proposed that depression is a heterogeneous syndrome that is not unitary and might be caused by distinct pathological processes. So, by using resting-state functional magnetic resonance imaging in a large multi-site sample (n = 1,188), the authors show that patients with depression can be subdivided into four subtypes defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. Further, the authors developed diagnostic classifiers and achieved high sensitivity and specificity (82%–93%) for the four depression subtypes in multi-site validation (n = 711) and out-of-sample replication (n = 477) data sets. More interestingly, the identified subtypes can predict the responsiveness to transcranial magnetic stimulation therapy, which indicates that the proposed biotypes are able to predict the treatment-response. Together, these preliminary reports from studies using cognitive testing, brain imaging, and/or genomic panels are discovering biologically meaningful subtypes of psychotic disorders. Although these results need further replication, they have demonstrated the potential to predict the prognosis and treatment response, important elements of validating biomarkers and establishing the potential for clinical application.

In summary, a mental disorder is a psychological syndrome that results from different biological processes. The idea of "biological subtypes" requires the integration of clinical data with other patient information, including genomics and neuroimaging, as well as physiological and behavioral characteristics, and then biologically stratify patients so as to improve diagnostics and therapeutics. Identifying the characteristics of these psychiatric biotypes may facilitate novel clinical and basic research and even implement biology-based psychiatric diagnosis.

References

1. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, *et al.* Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 2017, 23(1): 28–38. doi: 10.1038/nm.4246.
2. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016, 388: 1545–1602.

3. Hyman SE. Opinion - Can neuroscience be integrated into the DSM-V? Nat Rev Neurosci 2007, 8: 725–U716.
4. Insel TR, Cuthbert BN. Brain disorders? Precisely. Science 2015, 348: 499–500.
5. Karalunas SL, Fair D, Musser ED, Aykes K, Iyer SP, Nigg JT. Subtyping attention-deficit/hyperactivity disorder using temperament dimensions toward biologically based nosologic criteria. Jama Psychiatry 2014, 71: 1015–1024.
6. Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, *et al.* Identification of distinct psychosis biotypes using brain-based biomarkers. Am J Psychiatry 2016, 173: 373–384.