



Integrating Psychiatry and Medical Biotechnology as a Way to Achieve Scientific, Precision, and Personalized Psychiatry

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Abstract

Besides concerns about the increasing prevalence of psychiatric disorders and the significant burdens and costs, there are concerns about its validity. The dilemma of validity went so far that studies described the diagnoses in psychiatry as scientifically worthless. We suggest integrating psychiatry and medical biotechnology and using biotechnological products in psychiatric aspects help psychiatry become more precise, strengthen its position among other sciences, and increase its scientific credibility by giving examples. For this matter, we need different inputs to choose between the vast outputs. The most common inputs are clinical symptoms, cognitive function, individual and environmental risk factors, molecular markers, genetic markers, neuroimaging signs, and big data. Some molecular markers have been shown to have a relationship with psychiatric disorders such as Interleukin-6 (IL-6) and Tumor Necrosis Factor- α (TNF- α). Genetic studies might evolve the most accurate part of precision psychiatry. Currently, and through the developments in technology, genome-wide association studies have become available. In neuroimaging signs, psychiatric disorders are associated with generalized rather than focal brain network dysfunction, and functional magnetic resonance imaging could be performed to study them. It would exhibit different aberrancies in various psychiatric disorders. In big data, the constitution of predictive models and movement toward precision psychiatry can be led by using artificial intelligence and machine learning.

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Introduction

Today, the importance of psychiatry in the mental health of individuals and public health is evident. Psychiatric disorders that are highly prevalent and increasing cause patients' dysfunction, adverse effects on people in contact, isolation, reduced quality of life, the tendency to drugs and alcohol, and suicide, thereby imposing significant burdens and costs^{1,2}.

Validity is generally defined to the extent that a concept reflects the nature of reality and is measured precisely in quantitative studies. In assessing the validity of a theory, the definition of a concept is not enough, and the appropriate methodology for testing the concept should also be considered. This problem, which has clinical, moral, financial, and legal implications, has always been a significant concern in psychiatry³.

This dilemma went so far that studies described the accuracy of diagnosing most psychiatric disorders at about half and the diagnoses as scientifically meaningless and worthless^{4,5}. We aim to suggest biotechnology assistance to psychiatry and the integration of psychia-

try and medical biotechnology as a way out of this dilemma and achieve precision personalized psychiatry by giving examples.

Precision and Personalized Psychiatry

Precision psychiatry is an almost equal term for personalized psychiatry and is consists of using all health-related aspects of a patient to reach the best possible outcome⁶. For this matter, we need different inputs to choose between the vast therapeutic options. The most common types of these inputs are clinical symptoms, cognitive function, individual and environmental risk factors, molecular markers, genetic markers, neuroimaging signs, and big data^{7,8}. The combination could help the diagnosis, disease susceptibility, treatment (selection and dosage), and prognosis.

Clinical and environmental markers

The Diagnostic and Statistical Manual Mental Disorders 5 (DSM-5) and the International Classification of Diseases 10 (ICD-10) are the most useful classifica-

tion tools to diagnose psychiatric disorders. They provide an acceptable system to formulize the clinical presentations; however, the lack of specificity makes it challenging to identify the definite diagnosis. Several risk factors contribute to the evolution of a psychological disorder. History of trauma or serious illness and related medication, occupational and marital status, habits and lifestyle, presence of previous mental health disorders (especially during childhood and adolescence), genetic vulnerability, and family history of mental disorders (especially bipolar and psychotic disorders) could be a trigger for psychological disorders and might predict the prognosis⁹⁻¹⁴.

Molecular markers

More quantifiable data are necessary for precision psychiatry, and here we note some. The neurocognitive function could be assessed with tests measuring multiple domains, such as attention, memory, and cognitive control. Each of these domains might be altered in distinct diseases and may predict the illness severity¹⁵. Some molecular markers have been shown to have a relationship with psychiatric disorders. In a meta-analysis performed by Goldsmith *et al*, it was demonstrated that the levels of interleukin-6, tumor necrosis factor- α , serum soluble interleukine-2 receptor, and interleukine-1 receptor antagonist were significantly elevated in patients afflicted with acute presentation of schizophrenia, bipolar disorders, or major depressive disorder, in comparison with healthy controls. However, these results differed in chronically ill patients and those who received proper treatment, but significant changes in these markers were seen¹⁶. Wang *et al* also revealed that in patients with schizophrenia and bipolar disorders, the CSF interleukine-1 β and kynurenic acid levels increased, and in those with schizophrenia and major depressive disorder, interleukine-6 and interleukine-8 levels become higher. They also noted that many of these changes were in concordance with serum samples¹⁷. Some other biomarkers have been studied and shown to have a possible relationship with psychiatric disorders such as CRP levels, interleukine-3, interleukine-10, interleukine-12, interleukine-17, interleukine-18, interleukine-23, transforming growth factor- β , interferon- γ , serum glucose, lipid profile¹⁸⁻²⁰. These markers need further investigation to evaluate their efficacy and applicability before implementing in clinical practice.

Genetic markers

Genetic studies might evolve the most accurate part of precision psychiatry. At first, family studies and then twin studies scrutinized the hereditary phenotypes of mental health diseases; currently and through the developments in technology, genome-wide association studies have become available. These studies showed a correlation between genetic alterations in CACNA1C, NCAN, and ODZ4 and bipolar disorder. They also revealed nucleotide polymorphism in schizophrenia²¹.

It seems that depression and suicidal ideation could also be affected with some genes alteration such as CRHR1 and FKBP5^{23,24}. In a recently published study, Li *et al* used methylation microarray and pyrosequencing to detect methylation. They found that the DNA methylation of two CpG sites in LIME1 and one in SPTBN2 methylation could lead to attention deficit in children²⁵. Other suggested methylation sites related to attention deficit hyperactivity disorder (ADHD) are TRABP1, COMT, ANKK1, BDNF, NGFR, DPP10, and TPH2^{26,27}. Patients with some genetic syndromes like DiGeorge syndrome (micro-deletion on chromosome 22p11.2) could develop mental health issues (in this case: schizophrenia)²⁸.

Structural markers

Psychiatric disorders are supposed to be associated with generalized rather than focal brain network dysfunction²⁹. To study these networks, functional Magnetic Resonance Imaging (fMRI) could be performed. It would exhibit different aberrancies in various psychiatric disorders. Besides, distinct brain areas and networks could be afflicted in a specific presentation of a single disease. For example, schizophrenia can cause numerous symptoms, each probably related to a particular part³⁰. However, these changes do not have an exact diagnostic role yet but can predict the possible signs and prognosis³¹. Previous studies also used volumetric MRIs showing enlargement of the ventricles, specifically in schizophrenia, and reduction in hippocampus size, mainly in severe cases of depression, schizophrenia which are related to drug resistance and poorer outcome³²⁻³⁴. Yu *et al* conducted an MRI-based study on depressed patients and concluded that cortical thickness and subcortical volumes in the frontal lobe and limbic system negatively correlated with the level of anxious misery measures. Patients with more positive scores had more amygdala and hippocampal volumes and thickness of precuneus and cingulate cortex.

Pharmacogenetics

Pharmacogenetics (by studying CYP metabolism rate, target receptor polymorphisms, *etc.*) has been shown to be advantageous in patients respecting choosing the best medication and dosage and predicting the prognosis and adverse effects³⁵⁻³⁸.

Big data

Big data employ large databanks, electronic health records, and mobile devices data other than all of this information. Then by using artificial intelligence and machine learning, they can lead to the constitution of predictive models and movement toward precision psychiatry³⁹.

All of the mentioned data are representative cases of the more precise implications of patient's information; even if they are currently not fixed or feasible enough to be used worldwide, there is a possible future for them to benefit patients with psychiatric disorders.

Conclusion

Besides concerns about the increasing prevalence of psychiatric disorders and the significant burdens and costs associated with them, there are concerns about its validity. We suggested that integrating psychiatry and medical biotechnology and using biotechnological products in various aspects of psychiatry help psychiatry become more precise, strengthen its position among other sciences, and increase its scientific credibility.

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Conflict of Interest

The authors have no conflict of interest.

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Ethical Statement

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References

- Akhondzadeh S. Hippocampal synaptic plasticity and cognition. *J Clin Pharm Ther* 1999;24(4):241-8.
- Akhondzadeh S. The 5-HT hypothesis of schizophrenia. *IDrugs* 2001;4(3):295-300.
- Telles Correia D. Different perspectives of validity in psychiatry. *J Eval Clin Pract* 2017;23(5):988-93.
- Al-Huthail YR. Accuracy of referring psychiatric diagnosis. *Int J Health Sci (Qassim)* 2008;2(1):35-8.
- Allsopp K, Read J, Corcoran R, Kinderman P. Heterogeneity in psychiatric diagnostic classification. *Psychiatry Res* 2019;279:15-22.
- Perna G, Cuniberti F, Daccò S, Grassi M, Caldirola D. 'Precision' or 'personalized' psychiatry: different terms - same content? *Fortschr Neurol Psychiatr* 2020;88(12):759-66.
- Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry'. *BMC Med* 2017;15(1):80.
- Wium-Andersen IK, Vinberg M, Kessing LV, McIntyre RS. Personalized medicine in psychiatry. *Nord J Psychiatry* 2017;71(1):12-9.
- Itoh M, Yonemoto T, Ueno F, Iwahara C, Yumoto Y, Nakayama H, et al. Influence of comorbid psychiatric disorders on the risk of development of alcohol dependence by genetic variations of ALDH2 and ADH1B. *Alcohol Clin Exp Res* 2020;44(11):2275-82.
- Chung KH, Li CY, Kuo SY, Sithole T, Liu WW, Chung MH. Risk of psychiatric disorders in patients with chronic insomnia and sedative-hypnotic prescription: a nationwide population-based follow-up study. *J Clin Sleep Med* 2015;11(5):543-51.
- Myllyaho T, Siira V, Wahlberg KE, Hakko H, Tikkanen V, Läksy K, et al. Dysfunctional family functioning in high socioeconomic status families as a risk factor for the development of psychiatric disorders in adoptees: the Finnish Adoptive Family Study of Schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 2021.
- Paananen R, Tuulio-Henriksson A, Merikukka M, Gissler M. Intergenerational transmission of psychiatric disorders: the 1987 Finnish Birth Cohort study. *Eur Child Adolesc Psychiatry* 2021;30(3):381-9.
- Dewa CS, Lin E, Koehoorn M, Goldner E. Association of chronic work stress, psychiatric disorders, and chronic physical conditions with disability among workers. *Psychiatr Serv* 2007;58(5):652-8.
- Clous EA, Beerthuisen KC, Ponsen KJ, Luitse JSK, Olff M, Goslings JC. Trauma and psychiatric disorders: A systematic review. *J Trauma Acute Care Surg* 2017;82(4):794-801.
- Millan MJ, Agid Y, Brüne M, Bullmore ET, Carter CS, Clayton NS, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov* 2012;11(2):141-68.
- Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry* 2016;21(12):1696-709.
- Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. *Schizophr Bull* 2018;44(1):75-83.
- Bekhat M, Chu K, Le NA, Woolwine BJ, Haroon E, Miller AH, et al. Glucose and lipid-related biomarkers and the antidepressant response to infliximab in patients with treatment-resistant depression. *Psychoneuroendocrinology* 2018;98:222-9.
- Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry* 2011;70(7):663-71.
- Reale M, Costantini E, Greig NH. Cytokine imbalance in schizophrenia. From research to clinic: potential implications for treatment. *Front Psychiatry* 2021;12:536257.
- Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* 2011;43(10):977-83.
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;511(7510):421-7.
- Hernández-Díaz Y, González-Castro TB, Juárez-Rojop IE, Tovilla-Zárate CA, López-Narváez ML, Genis-Mendoza AD, et al. The role of rs242941, rs1876828, rs242939 and rs110402 polymorphisms of CRHR1 gene and the depression: systematic review and meta-analysis. *Genes Genomics* 2021.

24. De la Cruz-Cano E. Association between FKBP5 and CRHR1 genes with suicidal behavior: A systematic review. *Behav Brain Res* 2017;317:46-61.
25. Li SC, Kuo HC, Huang LH, Chou WJ, Lee SY, Chan WC, et al. DNA methylation in LIME1 and SPTBN2 genes is associated with attention deficit in children. *Children (Basel)* 2021;8(2).
26. Heinrich H, Grunitz J, Stonawski V, Frey S, Wahl S, Albrecht B, et al. Attention, cognitive control and motivation in ADHD: Linking event-related brain potentials and DNA methylation patterns in boys at early school age. *Sci Rep* 2017;7(1):3823.
27. Weiß AL, Meijer M, Budeus B, Pauper M, Hakobjan M, Groothuisink J, et al. DNA methylation associated with persistent ADHD suggests TARBP1 as novel candidate. *Neuropharmacology* 2021;184:108370.
28. Bassett AS, Chow EW, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R. The schizophrenia phenotype in 22q11 deletion syndrome. *Am J Psychiatry* 2003;160(9):1580-6.
29. Barch DM. Resting-state functional connectivity in the human connectome project: current status and relevance to understanding psychopathology. *Harv Rev Psychiatry* 2017;25(5):209-17.
30. Gratton C, Kraus BT, Greene DJ, Gordon EM, Laumann TO, Nelson SM, et al. Defining individual-specific functional neuroanatomy for precision psychiatry. *Biol Psychiatry* 2020;88(1):28-39.
31. Keshavan MS, Collin G, Guimond S, Kelly S, Prasad KM, Lizano P. Neuroimaging in schizophrenia. *Neuroimaging Clin N Am* 2020;30(1):73-83.
32. Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull* 2013;39(5):1129-38.
33. Sayo A, Jennings RG, Van Horn JD. Study factors influencing ventricular enlargement in schizophrenia: a 20 year follow-up meta-analysis. *Neuroimage* 2012;59(1):154-67.
34. Lorenzetti V, Allen NB, Fornito A, Yücel M. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *J Affect Disord* 2009;117(1-2):1-17.
35. Bättig VAD, Roll SC, Hahn M. Pharmacogenetic testing in depressed patients and interdisciplinary exchange between a pharmacist and psychiatrists results in reduced hospitalization times. *Pharmacopsychiatry* 2020;53(4):185-92.
36. Pérez V, Salavert A, Espadaler J, Tuson M, Saiz-Ruiz J, Sáez-Navarro C, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC Psychiatry* 2017;17(1):250.
37. Peterson K, Dieperink E, Anderson J, Boundy E, Ferguson L, Helfand M. Rapid evidence review of the comparative effectiveness, harms, and cost-effectiveness of pharmacogenomics-guided antidepressant treatment versus usual care for major depressive disorder. *Psychopharmacology (Berl)* 2017;234(11):1649-61.
38. Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based approach. Part II: Clinical pharmacology and therapeutic monitoring. *CNS Drugs* 2009;23(4):331-49.
39. Winter NR, Hahn T. [Big data, AI and machine learning for precision psychiatry: How are they changing the clinical practice?]. *Fortschr Neurol Psychiatr* 2020;88(12):786-93. German.