

The Future of Psychiatry

O Futuro da Psiquiatria

Joana Reis Correia^{1*}, Tânia B Cavaco², Joana Catanho³

*Autor Correspondente/Corresponding Author:

Joana Correia [joana.correia2@chlc.min-saude.pt]

ORCID iD: 0000-0003-1211-5414

PALAVRAS-CHAVE: Farmacogenética; Medicina de Precisão; Perturbações Mentais; Saúde Mental

KEYWORDS: Mental Disorders; Mental Health; Pharmacogenetics; Precision Medicine

INTRODUCTION

Psychiatry has been an evolving field in medicine, but current diagnostic and prognostic criteria, as well as available treatments are still in need of scientific improvement and optimized approaches. There is a rising interest and global curiosity regarding future outcomes and developments in psychiatry, but overall, the goal in psychiatry seems to, just like any other field in medicine, achieve precision psychiatry with more advanced diagnostic tools and personalized treatment interventions.

Current psychiatric research needs to address two big challenges: a shift in traditional diagnostic systems on the one hand, and on the other, the yet insufficient comprehension and insight regarding the biology and pathophysiology of psychiatric disorders. Although

modern neuroimaging techniques have allowed for many new insights on brain pathways, brain areas and circuit dysfunction which may underlie psychiatric disorders, these insights have not been systematically linked to the prediction of clinical outcomes and have also not been delivered into the hands of clinicians to an actionable system for improving patients' lives.¹

Psychiatric syndromes are generally referred to as "disorders" (illnesses that disrupt normal function) and only a few are considered "diseases" (disorders with known pathophysiology or structural pathology). An obvious goal of psychiatric research is to convert idiopathic disorders into pathophysiological-defined diseases.² It has been argued that identical changes in neural dynamics may produce different behavioral outputs depending on the environment. This may ex-

1. Child and Adolescent Psychiatry resident, in Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal. 2. Child and Adolescent Psychiatry resident, in Hospital Garcia de Orta, Almada, Portugal. 3. Medical Genetics resident in Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal.

Recebido/Received: 2023/10/29 - Aceite/Accepted: 2024/01/19 - Publicado online/Published online: 2024/02/21

© Author(s) (or their employer(s)) and Gazeta Médica 2024. Re-use permitted under CC BY-NC 4.0. No commercial re-use. © Autor (es) (ou seu (s) empregador (es)) e Gazeta Médica 2024. Reutilização permitida de acordo com CC BY-NC 4.0. Nenhuma reutilização comercial.

plain why only a subgroup of patients respond to a drug or psychotherapeutic treatment approved for any given disorder. Therefore, to create more personalized and more targeted forms of therapy, a different characterization of the pathophysiological mechanisms is required, one which may supplement categorical conventional diagnoses.³

THE SHIFT IN DIAGNOSTIC SYSTEMS

Traditional diagnostic systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM, currently in its 5th edition) and the International Classification of Diseases (ICD, currently in its 11th Edition) do not explain the underlying biopsychosocial processes of mental illness, nor do they drive clinical developments.⁴ The core issue potentially responsible for the limitations of traditional taxonomies is that its construction had gone beyond the evidence available on the structure of psychopathology, and it was shaped by several other considerations. It appears that this rational approach to psychiatric nosology, not grounded in structural research nor in the etiologic architecture of mental disorders, has failed to represent psychopathology accurately.⁵

To date, most studies focusing on the neural bases of psychiatric disorders use categorical diagnostic systems, but neurobiological changes are now increasingly recognized as being more strongly related to combinations of different dimensions of psychopathology, than to general clinical labels.⁶ The sluggish pace of discovery in psychiatry has been, in part, attributed, to the limited validity and certain arbitrariness of traditional diagnoses. A solution to the shortcomings of traditional taxonomies is emerging as a quantitative nosology - an empirically based organization of psychopathology.⁵

A NEW TAXONOMY

Research to date has focused on case control comparisons of diagnostic groups of psychiatric disorders defined by traditional symptom criteria. Findings from case control studies tend to be inconsistent, and this inconsistency is not surprising, given the heterogeneity of most psychiatric disorders.⁷

The understanding of the role that brain circuits and their activation play in clinical psychiatric dysfunction and its manifestations is still limited, and advances in exploring human neuroimaging circuits involved in

psychiatric disorders may provide the foundations for formulating a new taxonomy.

Despite the current, narrow clinical impact of many neuroimaging methods, there is hope that imaging along with new machine learning applications may come to accelerate the recognition of subtle but informative brain patterns in functional imaging data, which may contribute to more optimized diagnoses, prognoses, and treatment monitoring and response, in psychiatric and neurodevelopmental disorders in the future.⁸

THE ROLE OF BIOMARKERS

Although still in their infancy, biomarkers hold the promise of bringing even greater precision and even better outcomes in mental health, some of the promising systems that are being assessed as sources of biomarkers include genomic, proteomic, metabolomic, and immunologic processes.⁹ As our understanding of basic cellular biology, function, and communication in the normal and disordered central nervous system grows, so will the number of potential biomarkers.⁹

Currently, it is not clear what role genomics and biomarkers will have in the diagnosis of mental illnesses, or in the diagnosis of people at-risk for mental illnesses. The application of new tests for clinical diagnoses of mental illnesses is proving problematic because diagnoses in mental health are based on categorical systems.¹⁰

However, some interesting studies have been published, namely, a prospective study of 2600 war zone-deployed Marines, published in 2014, found that a marker of peripheral inflammation, plasma C-reactive protein, may be prospectively associated with PTSD symptom emergence, suggesting that inflammation may predispose to post-traumatic stress disorder.¹¹ Studies in the past decades have noted complex interactions between the immune system, systemic inflammation, and the brain, which can lead to changes in mood, cognition, and behavior, with more robust epidemiological and genetic studies establishing a possible association between schizophrenia and the immune system.¹²

In a study published in 2012, the authors measured gene and protein expression levels of proinflammatory cytokines interleukin (IL)-1 β , IL-6, and tissue necrosis factor (TNF)- α , in the prefrontal cortex (PFC) of both 24 teenage suicide victims and 24 matched normal control subjects (whose death was not by suicide). Results showed that mRNA and protein expression levels of IL-1 β , IL-6, and TNF- α were significantly increased

in the Brodmann area 10 of the prefrontal cortex of suicide victims, compared to normal control subjects. These findings suggest an important role for IL-1 β , IL-6, and TNF- α in the pathophysiology of suicidal behavior and that proinflammatory cytokines may be an appropriate target for developing therapeutic agents.¹³

In a study published in 2018, antidepressant treatment resistance was found to be associated with increased inflammatory markers in patients with major depressive disorder, suggesting that measuring these markers and targeting inflammation or its downstream mediators may be relevant when considering treatment options for depressed patients with multiple failed antidepressant treatment trials in their current depressive episode.¹⁴

THE ROLE OF GENOMICS

Even though there is no comprehensive portrait of genetic architecture, psychiatric disorders are known to be polygenic, encompassing both common and rare variants. How these variants combine to influence disease pathogenesis and phenotypic heterogeneity is not yet known.²

Acquiring more knowledge on the identification of a genetic variation as well as its frequency, and the suggested impact at each locus - would be of exceptional importance. This information could catalyze an array of specific scientific studies, which may allow for: the elucidation of biological mechanisms between the genotype and the psychiatric phenotype; the assessment of gene action over development; help in addressing the critical roles of gene-gene and gene-environment interactions and better understanding the role played by epigenetic modifications. The genomic search space is extensive but finite, and so, with the right tools there is potential to discover the above-mentioned mechanisms.¹⁵

In a recent meta-analysis of the whole exome of almost 25 000 schizophrenia cases, ultra-rare coding variants in 10 genes were identified as conferring substantial risk for schizophrenia. This study also provided support for dysfunction of the glutamatergic system as a hypothesis in the pathogenesis of schizophrenia (adding to the dopaminergic hypothesis already known).¹⁶

The availability of polygenic risk scores, providing risk assessment for psychiatric disorders, has pushed this type of testing to the forefront-leaving to the consideration of clinicians if, when and how to apply or manage them in clinical settings. Psychiatric genetic counseling will not represent a fundamental paradigm shift; these tests cannot diagnose a psychiatric dis-

order, nor can they determine whether someone will develop one. Any testing applied in a psychiatric genetic counseling context will be, at best, probabilistic information on risk and must still be applied in the context of a decision that addresses patient's emotional issues-guilt, blame, shame, fear, and stigma-that are so often attached to people's explanations for cause of illness.¹⁷ The possibility of fatalistic thinking and fear of the future, alongside the subsequent potential social implications such as stigmatization, needs careful consideration in communicating such results.¹⁸ Even if better and more accurate polygenic risk scores are developed in the future, a holistic discussion of how both genetic and environmental factors may contribute to the condition will always be desired.¹⁷

NEW TECHNOLOGIES

Imaging technologies that can expand imaging into more ecological environments, particularly for longer duration imaging, would be of great utility since conventional neuroimaging only collects data for a short amount of time and psychiatric disorders and its changes imply a longer timeframe. A sort of "Holter monitor" for the brain that could be sent home with a patient and collect data for many hours or days may have the potential for radical new insights into brain function.⁸

Measuring daily behavior using personal smart devices, often referred to as "digital phenotyping" could also be a way of recognizing natural behavioral patterns, which could potentially assist clinicians in revealing subtle early signs for interpersonal difficulties, before symptoms develop into a fully-fledged psychiatric disorder.⁶

Insights combining behavioral and neuroimaging markers of psychopathology may be key for detecting clinically applicable biomarkers for psychiatric disorders that can feedback into clinical practice and enable novel insights into the brain mechanisms underlying individual psychopathology.⁶

CURRENT TREATMENT IS NOT ENOUGH

Current treatments, which consist mostly of psychopharmacology and psychotherapy, still offer suboptimal responses.¹⁰ Studies show that people suffering from severe mental health conditions die 10 to 20 years earlier than the general population, with globally mental disorders account for 1 to 6 years lived with disability.¹⁹

Psychopharmacology has only developed as a discipline in the mid-20th century. Before that, psychiatric

drugs were accidentally discovered in clinical observations of patients, who were often being treated for other conditions.²⁰ Even though current treatment guidelines may benefit some patients, treatment resistant patients and their prescribers are left to ponder, “What do we do when there is no further scientific evidence regarding treatment options?” in the current classical model of psychiatric practice.¹⁰ And to answer that question there is an emerging approach towards precision medicine consisting of pharmacogenomics tailoring drug selection and dosing to the patient’s genetic features.²¹

It is highly unlikely that any single test will ever dictate what drug is best to prescribe or not, in most cases. Pharmacogenomic test results orients the advanced prescriber’s rationale along a neurobiological perspective in selecting treatments that are biologically plausible, rather than just using intuition, habit, or trial and error.

Pharmacogenomic “precision” testing can potentially guide the clinician in drug selection, especially in treatment-resistant patients, and currently includes state-of-the-art pharmacokinetic and pharmacodynamic genomic markers, with epigenetic and other biomarkers being made available to enter clinical practice as well.¹⁰

CONCLUSION

Current treatment options in psychiatry are not enough. There are still many unanswered questions regarding the pathophysiological mechanisms underlying psychiatric disorders. This knowledge may unveil the path to a clinical practice of precision psychiatry with more effective and more tailored treatments. There are a lot of potential new investigations and studies regarding neuroimaging, biomarkers, and genomics, especially considering the power of new technology coming up.

To move forward into a more optimized, precision psychiatry, it will be necessary to undertake larger, multi-site investigations resorting to standardized protocols, integrative analytic models, and databases.⁷

DECLARAÇÃO DE CONTRIBUIÇÃO /CONTRIBUTORSHIP STATEMENT

JRC: Conceção do estudo e escrita do artigo

TC e JC: Revisão do artigo

Todos os autores aprovaram a versão final a ser publicada

JRC: Study design and article writing

TC and JC: Article review

All authors approved the final version to be published

RESPONSABILIDADES ÉTICAS

CONFLITOS DE INTERESSE: Os autores declaram não possuir conflitos de interesse.

SUORTE FINANCEIRO: O presente trabalho não foi suportado por nenhum subsídio ou bolsa.

PROVENIÊNCIA E REVISÃO POR PARES: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

FINANCIAL SUPPORT: This work has not received any contribution grant or scholarship.

PROVENANCE AND PEER REVIEW: Not commissioned; externally peer reviewed.

REFERENCES

1. Goldstein-Piekarski AN, Ball TM, Samara Z, Staveland BR, Keller AS, Fleming SL, et al. Mapping Neural Circuit Biotypes to Symptoms and Behavioral Dimensions of Depression and Anxiety. *Biol Psychiatry*. 2022;91:561-71. doi: 10.1016/j.biopsych.2021.06.024.
2. Gratten J, Wray NR, Keller MC, Visscher PM. Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nat Neurosci*. 2014;17:782-90. doi: 10.1038/nn.3708.
3. Koppe G, Meyer-Lindenberg A, Durstewitz D. Deep learning for small and big data in psychiatry. *Neuropsychopharmacology*. 2021;46:176-90. doi: 10.1038/s41386-020-0767-z.
4. Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic Approaches to Mental Health Problems: Current Status and Future Directions. *J Consult Clin Psychol*. 2020;88:179-95. doi: 10.1037/ccp0000482.
5. Kotov R, Waszczuk MA, Krueger RF, Forbes MK, Watson D, Clark LA, et al. The hierarchical taxonomy of psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol*. 2017;126:454-77. doi: 10.1037/abn0000258.
6. Lahnakoski JM, Eickhoff SB, Dukart J, Schilbach L. Naturalizing psychopathology—towards a quantitative real-world psychiatry. *Mol Psychiatry*. 2022;27:781-3. doi: 10.1038/s41380-021-01322-8.
7. Williams LM, Goldstein-Piekarski AN. Applying a neural circuit taxonomy in depression and anxiety for personalized psychiatry. In: *Personalized Psychiatry*. Amsterdam: Elsevier; 2019. p. 499-519.
8. Anderson AN, King JB, Anderson JS. Neuroimaging in Psychiatry and Neurodevelopment: why the emperor has no clothes. *Br J Radiol*. 2019;92:20180910. doi: 10.1259/bjr.20180910.

9. Rush AJ, Ibrahim HM. A Clinician's Perspective on Biomarkers. *Focus*. 2018;16:124–34.
10. Stahl SM. Psychiatric Pharmacogenomics: How to Integrate into Clinical Practice. *CNS Spectr*. 2017;22:1–4. doi: 10.1017/S109285291600095X.
11. Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, et al. Assessment of plasma C-Reactive protein as a biomarker of posttraumatic stress disorder risk. *JAMA Psychiatry*. 2014;71:423–31.
12. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. *Lancet Psychiatry*. 2015;2:258–70. doi: 10.1016/S2215-0366(14)00122-9. E
13. Pandey GN, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC, et al. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res*. 2012;46:57–63.
14. Haroon E, Daguanno AW, Woolwine BJ, Goldsmith DR, Baer WM, Wommack EC, et al. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder HHS Public Access. *Psychoneuroendocrinology*. 2018;95:43–9. doi: 10.1016/j.psyneuen.
15. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: The emerging picture and its implications. *Nat Rev Genet*. 2012;13:537–51. doi: 10.1038/nrg3240.
16. Singh T, Poterba T, Curtis D, Akil H, Al Eissa M, Barchas JD, et al. Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature*. 2022;604:509–16. doi: 10.1038/s41586-022-04556-w.
17. Austin JC. Evidence-based genetic counseling for psychiatric disorders: A road map. *Cold Spring Harb Perspect Med*. 2020;10:a036608. doi: 10.1101/cshperspect.a036608.
18. Baldwin H, Loebel-Davidsohn L, Oliver D, Salazar de Pablo G, Stahl D, Riper H, et al. Real-World Implementation of Precision Psychiatry: A Systematic Review of Barriers and Facilitators. *Brain Sci*. 2022;12:934. doi: 10.3390/brainsci12070934.
19. World Health Organization. World mental health report: transforming mental health for all [Internet]. Geneva; 2022 [cited 2023 Apr 29]. Available from: <https://www.who.int/publications/i/item/9789240049338>.
20. Robinson E. Psychopharmacology: From serendipitous discoveries to rationale design, but what next? *Brain Neurosci Adv*. 2018;2:239821281881262.
21. Cecchin E, Stocco G. Pharmacogenomics and personalized medicine. *Genes*. 2020;11:679. doi: 10.3390/genes11060679.