The future of psychiatric research

O futuro da pesquisa em psiquiatria

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Abstract

Psychiatric disorders place considerable burden on individuals and on public health. Funding for research in psychiatry is less than ideal, but even so high quality research is being conducted at many centers. However, these studies have not impacted clinical practice as much as expected. The complexity of psychiatric disorders is one of the reasons why we face difficulties in translating research results to patient care. New technologies and improved methodologies are now available and must be incorporated to deal with this complexity and to accelerate the translational process. I discuss the application of modern techniques for data acquisition and analysis and also the new possibilities for performing trials in virtual models of biological systems. Adoption of new technologies is necessary, but will not reduce the importance of some of the fundamentals of all psychiatry research, such as the developmental and translational perspectives. Psychiatrists wishing to integrate these novelties into their research will need to work with contributors with whom they are unaccustomed to working, such as computer experts, a multidisciplinary team, and stakeholders such as patients and caregivers. This process will allow us to further understand and alleviate the suffering and impairment of people with psychiatric disorders.

Keywords: Research, trends, psychiatry.

Resumo

Os transtornos psiquiátricos são responsáveis por uma significativa carga de doença tanto no nível individual quanto na saúde pública. Mesmo com financiamento abaixo do ideal, muitas pesquisas de alta qualidade vêm sendo executadas em vários centros. Entretanto, o impacto desses estudos na prática clínica é menor que o esperado. A complexidade dos transtornos psiquiátricos é uma das razões pelas quais enfrentamos tanta dificuldade na translação dos resultados das pesquisas para a prática clínica. Novas tecnologias e metodologias aperfeiçoadas já estão disponíveis e devem ser incorporadas para lidar com esta complexidade e acelerar o processo translacional. Discuto, neste artigo, a aplicação de técnicas modernas para a coleta e análise de dados e as novas possibilidades para a realização de testes em modelos virtuais dos sistemas biológicos. A adoção das novas tecnologias é necessária, mas não reduzirá a importância de fundamentos da pesquisa em psiquiatria, como as perspectivas desenvolvimental e translacional. Os psiquiatras que desejarem integrar essas novas tecnologias à suas pesquisas terão que trabalhar com colaboradores com os quais não estão acostumados, como especialistas em informática, equipes multidisciplinares e representantes de partes interessadas nos resultados, como pacientes e provedores de cuidados assistenciais. Esse processo permitirá um avanço no conhecimento e no alívio do sofrimento e da incapacidade das pessoas com transtornos psiquiátricos.

Descritores: Pesquisa, tendências, psiquiatria.

Psychiatric disorders have a major impact on overall health and are associated with suffering, functional impairment, morbidity and early mortality. The latest version of the Global Burden of Disease study ranks mental disorders and substance use disorders as the fifth-placed group based on global burden and ranks them first based on years living with disability.[1] Mortality data show that psychiatric patients live from 10 to 20 years less than the general population.[2,3] These data should make psychiatric research a priority within health

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research, but this is not yet the case, at least when considered in terms of the amount of funding available for psychiatric research in relation to other fields.[3]

Currently, the contributions to patient care made by developments from research are very limited. Mortality rates haven't been reduced.[4] Even suicide death rates remain stable and are rising among some populations.[5] The emergence of new treatments based on new mechanisms is also extremely limited. Few new drugs have been developed in recent years, and most of those that have been are improved versions of existing ones and not genuine innovations. Moreover, the search for biomarkers that could be used to help diagnosis and planning of treatment has still not yielded results that can be widely applied in clinical practice.

Insufficient funding may be one of the causes of these limitations, but it is certainly not the only cause, since much high-quality research has been conducted with the financial resources that are available. There are other factors that also help to explain these difficulties. The central nervous system is very complex. Moreover, mental disorders result from interactions between biological factors and numerous environmental factors, making analysis even more complex.[4,6] Much research uses official classification systems, in particular the Diagnostic and Statistical Manual of Mental Disorders (DSM). These systems tend to group very different clinical conditions that probably have different underlying physiopathology under the same diagnoses. Furthermore, the opposite can also happen: clinical conditions that are diagnosed as distinct disorders can share the same physiopathology, but present differently in different patients.[7-11] Thus, the results of searching for the biological basis of a given diagnostic category tend to be inconclusive.

That said, it is clear that not only must psychiatric research efforts be maintained, they must be intensified. However, if we are to achieve more satisfactory results, we have to make progress in the way we do research. We cannot expect innovative outcomes if we are always using the same techniques. Three interesting publications on this subject give us an overview of how this future has been projected. Two of these are articles that collect the views of important experts in Mental Health. The first presents the challenges to be dealt with in the field of mental health around the world,[12] while the second presents the priorities for psychiatric research in Europe.[3] The third publication is the latest version of the Strategic Plan for Research, published by the National Institute of Mental Health (NIHM), which also defines which projects are priorities for receiving NIHM funding.[2]

Many of the views presented are common to all three publications. These include the need to understand the etiology and physiopathology of psychiatric disorders to be able to develop better treatments; trying to identify preventative interventions as well as efforts for mental health promotion; taking a developmental perspective on psychiatry disorders, identifying the trajectories of diseases and periods during which interventions will be more effective, as well as periods during which negative factors may be more harmful; and including innovative findings and technologies from other fields in research and in development of interventions.

Moreover, all three publications are concerned with the impact research has on public health, encouraging initiatives that accelerate the translational process, open up access to treatment for people with lower socioeconomic status, and provide feedback on research by assessing the result of such measures.

Many recent advances are already being incorporated into psychiatric research, giving us confidence that these objectives are attainable, at least to a great extent. In the following paragraphs I will address some of these advances: biological data scanning technologies, called 'omics', such as genomics, transcriptomics, proteomics, metabolomics, and connectomics; biological systems and analysis of biological networks; and technologies for acquisition, storage and processing of large-scale data, known as 'big data'.

Genome-wide association studies (GWAS) are a major technological advance and offer rapid assessment of thousands, even millions, of polymorphisms in a single patient for a relatively low cost.[13] Development of this technology in combination with mapping of the human genome raised high expectations about the possibility of discovering the genetic bases of diseases, including mental disorders. Unfortunately, to date, these expectation have not been realised.[14] Limitations including the small effect of each polymorphism, the multifactorial origin of mental disorders, the difficulty of assessing the validity of findings, the statistical difficulties involved in handling multiple comparisons, and the aforementioned limitations of the diagnostic systems have hindered this research to date.[15] However, while many results haven't been replicated, making us question their validity, some interesting results have been obtained. For example, these studies seem to indicate a common genetic basis for many psychiatric disorders.[4,7,16] This could strengthen the hypothesis that some diseases which are considered distinct might actually be different clinical manifestations of the same underlying disease. One very interesting recent study sought to assess the genetic basis of schizophrenia as a whole, and of its subtypes, by means of GWAS.[17] Instead of attempting to identify associations between specific polymorphisms and the diagnosis, this study first aimed to employ complex data analysis processes to identify

groups of polymorphisms that cluster in both patients and controls and also groups of phenomenological manifestations of schizophrenia in subsets of patients. Later, these data were cross-referenced and the results were tested in new samples in order to replicate and validate the findings. The researchers identified 42 groups of polymorphisms associated with a 70% risk of schizophrenia, which is a much higher percentage than achieved in any of the findings of other traditional GWAS studies. The researchers also identified associations between groups of polymorphisms and the subtypes of schizophrenia identified by phenomenological analysis. This study is an example of how innovative ways of using existing technologies can enrich research. Another way of improving the performance of GWAS studies is by jointly analyzing groups of polymorphisms that are related to a metabolic pathway possibly associated with a disorder. Another possibility is to look for associations with more homogeneous neuropsychiatric constructs with greater validity, instead of using the traditional diagnostic categories. This strategy allows for identification of the genetic bases of these constructs as well as their pathological effects, which are manifest in the clinical disorders. The application of GWAS to studies of gene-environment interactions is also an opportunity for new research, as current research into these interactions focuses on just one or a small number of polymorphisms.[18]

Another reason why the results of GWAS studies haven't yet fulfilled expectations is that many complex processes occur between genes and phenotypic expression and these processes are fundamental to the outcomes. For this reason, technologies have been developed that also perform wide-ranging assessments at other levels of biological phenomena, thereby allowing broad data to be gathered at each of these levels. Epigenomics assesses changes to DNA that determine whether a gene will be expressed or not,[19] transcriptomics assesses the results of transcriptions in the form of RNA,[20] and proteomics investigates the results of transcriptions in the form of proteins.[20] Another promising area for psychiatric research is connectomics, which is a field of knowledge that studies the connections between neurons and brain circuits. Its importance lies in the fact that the brains of psychiatric patients do not exhibit major structural changes. It is therefore likely that the dysfunctions responsible for symptoms are related to the way these circuits work.[21]

'Systems biology' is a new field of science with great potential to make considerable contributions to psychiatric research. The aim is to develop computational models of the existing systems of living organisms. The main strategy consists of modeling the behavior of molecules and intracellular metabolic pathways in order to understand cells, the connections between cells, tissues, and organs, and, ultimately, to understand the organism as a whole and its relationship with the environment. Computer-derived results are tested in experiments on living subjects or biological material and the results of these experiments are then used to confirm or correct the model, with the ideal goal of completely reproducing the functioning of the biological system in computer models.[22] This is a field of knowledge with interfaces between biology, mathematics, physics, chemistry, and computer science. The data generated by these systems are very complex. Mathematical and statistical methods for data analysis and generation of models are reliable and advanced enough to allow biological systems to be studied. Nevertheless, interpretation of results, correlation of different experiments, and selection of data with practical uses are all difficult. Notwithstanding, some of the results generated by these systems have already been confirmed in studies of gene transcription and metabolic pathways. These systems use the concept of biological networks, that is, the interconnections between different points of a metabolic system and their correlations with other systems. If we can decipher the biological networks linked to a given disorder, experiments conducted in these systems (known as 'in silico' experiments) may enable us to discover targets for new drugs, and predict their side effects and pharmacokinetics. It will also be easier to evaluate whether drugs which are effective for a particular condition can be used in another that involves similar biological networks.[23] This could reduce costs and accelerate the development of new treatments.

Both the 'omics' and biological systems approaches generate huge amounts of data that cannot be processed by human beings. Data analysis technologies are therefore a necessity. These technologies are already being developed and used in the field of healthcare, but are more widespread in other areas, such as economics, physics, and computer science, especially for analysis of so-called big data. The characteristics of big data are huge volumes, acquisition at high speed, and great variability.[24,25] In the field of healthcare many other sources are used besides data from omics. Healthcare services, for instance, collect data by means of electronic health records, imaging exams, and from information on health financing. Patients themselves generate data performing daily activities via the Internet, with smartphones, using devices with sensors, and with monitoring tools. Data collection and analysis pose a challenge, but also an opportunity. The volume of digital data produced nowadays is huge and within the field of healthcare it grows at a rate of 50% every year.[26] Analysis

of this data can provide results that it would not be possible to derive from clinical trials, such as drug safety evaluations after a drug has already been introduced in the market. They can also be used to help to generate knowledge about rare diseases and outcomes, assess extrapolation of data obtained in small samples, collect data for situations that have not been tested in trials, and conduct epidemiological surveys or surveys of secular trends of disease.[24] Some authors believe that the volume of information gathered by means of these methods will offer access to causal relations between exposures and outcomes, although this seems less likely.[24,26] There are also major limitations to using these large-scale sources of data in research. A great deal of these data are not collected with predetermined objectives and so could be of dubious quality for research purposes. The huge volume of data generates considerable background noise, making selection of relevant data difficult. Data analysis techniques such as data mining and machine learning are of great help in finding consistent outcomes within these data, but interpretation of these data is still reliant on human efforts and is very complex.

While creative and innovative studies can answer relevant questions, some phenotypes in psychiatry are overly complex and result from a huge variety of factors, many of them with very small effect sizes. Achieving comprehensive understanding of the environmental and genetic factors that shape the function and structure of the human brain may demand that the technologies available for neuroscientific studies be integrated and applied to large population-based samples. This is a method that some authors call population neuroscience.[27]

Including these and other technologies in psychiatric research is necessary. We cannot, however, transfer all our efforts to these methods. Other high-quality methods that have already been validated should continue to be employed and improved. It is unlikely that big data obtained in a non-systematic manner will ever replace well-designed epidemiological studies. Clinical trials will still be needed to test drugs developed using biological systems. Omics data will not replace understanding of the development and social interactions of patients.

Thus, I believe that in the future psychiatric research will have to integrate different methodologies and lines of thought. We must not forget what happened when the majority of psychiatry focused exclusively on psychoanalysis, making progress in other fields significantly slower. We cannot make the opposite mistake and focus solely on highly technological biological data or become restricted to a single paradigm.

I also believe that, regardless of what methodologies and which research questions we are interested in, some parameters are fundamental to the future of psychiatric research. One of them is the developmental perspective. Half of mental disorders begin before the age of 15 and three-quarters before the age of 18.[3] Therefore, it is critical to understand both normal and pathological development in order to also understand psychiatric disorders among adults. Even disorders that have onset in adulthood may be delayed manifestations of early developmental abnormalities and would therefore also need to be studied from a developmental perspective.[28] High quality and thorough developmental data can only be acquired with longitudinal studies. That is why emphasis on these studies is growing both globally,[29] and in Brazilian research too.[30] It will also be important to maintain a translational focus, in order to both prioritize research that can eventually impact the health of individuals and populations and also to accelerate the process of translation of the findings of research to patient care. In view of the limitations of our diagnostic systems, I also believe that it will be necessary to carry out research that is not based on current diagnostic categories. Patients with different diagnoses should be studied together when one is trying to understand a finding that permeates these diagnoses. Variations in the dimensions of neuropsychiatric constructs between patients and healthy people must also be studied. These are some of the principles of the NIMH initiative called the Research Domain Criteria (RDoC), which aims to substantially change psychiatric diagnoses.[4,11]

It is also important to bear in mind that the ultimate goal of psychiatry is to bring benefits to patients, whether by reducing morbidity, mortality, and suffering or by promoting well-being. Therefore, no progress will truly be effective if it does not reach healthcare systems. This is the reason why, besides developing new interventions, the future of psychiatric research must also focus on conducting studies that identify which methods generate practical changes in patient care in an effective manner. Moreover, it is necessary to study whether effective treatments are actually effective in the real world. It will also be necessary to conduct research that reduces the cost of treatments, such as interventions carried out by non-experts, making treatments more affordable.

This greater integration of research into the real world also requires the integration of patients and clinicians during the research process, either by defining priorities and making suggestions to research projects or by becoming part of research groups.[31]

In short, I believe that there will be no room in the future of psychiatric research for research based on just a single area of expertise and that overlooks progress made in other fields. Researchers must be open to working with contributors with whom they are not used to working, such as computer experts, multidisciplinary

teams and other stakeholders, such as patients and caregivers. This approach tends to allow for a greater understanding of the very complex types of problems that Psychiatry deals with. Thus, we can deepen our understanding of normal development, of factors that cause developmental deviation, of ways of preventing it, and of ways of treating cases in which prevention was not possible. We can also make the results of academic progress reach as many people as possible, leading to reductions in disparities and promotion of growth.

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