

CHALLENGE 6 : EXPOSING THE ROOTS OF MENTAL DISORDERS

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NON-CSIC EXPERTS

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Abstract: Env.

Mental disorders have devastating and increasing impact in our societies. CSIC researchers face the challenge of determining the biological and social causes and consequences of these disorders, and of finding efficient therapies. To these aims, the collaborative effort of neuroscientists, neurologists, psychiatrists, psychologists and human and social scientists, the use and development of state-of-the-art technologies and the contact with patient associations and pharma industry are required.

Palabras clave:

Keywords: Mental disorders, behaviour, pharmacotherapy, brain stimulation, brain circuits, neuroimaging, mental health care, psychosocial causes, social stigma

EXECUTIVE SUMMARY

Mental disorders have devastating impact for individuals and communities and are leading cause of disability in developed countries. Despite significant advances in recent years in the understanding and treatment of these disorders, they are considered one of the most relevant public health problems in Spain and Europe. A number of circumstances make mental disorders particularly challenging to address. These include the poor

knowledge about their aetiology, the complexity and variability of symptoms, the high incidence and comorbidity, the difficult diagnosis, the limited therapies and public care and the social stigma.

The CSIC counts with excellent researchers, from basic neuroscientists to investigators in human and social sciences, who are approaching mental disorders from different perspectives. Basic neuroscience researchers aim at understanding how the brain processes emotions, thoughts and behaviour and the mechanisms by which these processes are altered in mental disorders. Translational researchers aim at using this knowledge to design and assess therapeutic approaches. Researchers in human and social sciences aim at answering questions such as what is dementia and at reasoning about the models for mental health care and their historical evolution.

To maintain and improve the scientific excellence and a leading position in the study of mental disorders the CSIC should implement a series of strategies. Among them, we identified as a priority to increase human resources and avoid their dispersion, to foster platforms and common services for the generation of suitable animal models, next generation sequencing (NGS), drug screening, big data analysis, neuroimaging and behaviour, and to facilitate the interaction with relevant stakeholders such as clinicians and hospitals, patient associations and pharma industry.

6.1 Introduction and general description

Brain diseases (mental and neurological disorders) represent a considerable medical, social and economic burden in Europe. With yearly costs of about 800 billion euros and an estimated 179 million people afflicted in 2010, brain diseases are an unquestionable emergency and a grand challenge for neuroscientists, according to the European Brain Council and the European College of Neuropsychopharmacology (Gustavsson et al., 2011; Diluca and Olesen, 2014). Brain research is at the forefront of science, but extensive work is still needed to understand brain functioning at molecular, cellular, and system levels as well as to unravel the pathogenesis of complex brain diseases. Brain research and brain diseases are relatively new terms.

Brain diseases were included in the global burden of disease study by the WHO (World Health Organization) (Murray et al., 1997; Olesen et al., 2003). They are responsible for 35% of Europe's total disease burden with one-third of all European citizens suffering from at least one brain disorder in the lifetime. These data were calculated in terms of so-called DALYs, or disability-adjusted life years. Several comprehensive studies have been carried out to date, which show that mood disorders and dementia represent the most

costly brain diseases for European society (see Figure 1) (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators).

Figure 1. Cost of brain diseases in Europe 2010

Mental disorders are defined as syndromes characterized by clinically significant disturbance that affect mood, thinking and behaviour (APA, 2013). Almost 300 different conditions have been listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). They show highly variable symptoms that may be persistent, relapsing and remitting, or even occur as a single episode.

The incidence of mental disorders is steadily growing and has a strong impact on quality of life. They are associated with considerable comorbidity and mortality. Among mental disorders the most frequent include depression, bipolar disorder, dementia, schizophrenia and epilepsy, affecting about 500 million people worldwide (WHO, 2000). Addictive behaviour is another mental disorder with growing incidence that has recently led to public health crisis such as the opioid epidemic in US with 70,000 drug overdose deaths reported in 2018 (ASPA, 2018).

With the improvement of diagnostic methods, the incidence of previously minority mental disorders has increased dramatically in recent years. This is the case of autism spectrum disorders (ASD) with a prevalence estimate in Europe of about 1-2%. Still, diagnosing mental illness is a more subjective endeavour than diagnosing other diseases. No blood test exists for depression; no X-ray can identify a child at risk of developing bipolar disorder. At least not yet.

The high rate of comorbidity adds complexity to the diagnosis of mental disorders. A large number of studies have revealed that patients with mental disorders have higher rates of physical illness (Leucht et al., 2007; Walker et al., 2015; Weisser et al., 2009) and suicide (Turecki et al., 2019) than the general population. Comorbidity –the presence of two or more diseases– within mental disorders is pervasive, and the risk persists over time.

Psychiatric disorders are frequently reported in neurodegenerative diseases. Anxiety, depression, dementia, cognitive impairment, and psychosis are highly correlated in Parkinson's disease and other synucleinopathies and are associated with a range of early non-motor symptoms. Similarly, highly prevalent (i.e. Alzheimer's disease, fronto temporal dementia) and rare (i.e. genetic diseases such as neuropathic lysosomal storage

disorders) neurodegenerative diseases show symptoms that mimic those seen in mental disorders confounding the diagnostic efforts.

Mental disorders are likely to have multiple etiological causes, including genetic and epigenetic, biological, psychological, social and environmental risk factors, i.e. stressful early life events, all may contribute to the development or progression of mental disorders (Arango et al., 2018). Different risk factors may be present at different ages, with risk occurring as early as during prenatal period (WHO, 2012). Age of disease debut varies, with ASD and epilepsy normally doing it in childhood, psychotic symptomatology and schizophrenia in adolescence period and depression or bipolar disorder in adulthood. We are far from understanding the interplay among these risk factors in mental disorders. Thanks to new tools in genetic and neuroimaging, scientists are making progress toward deciphering details of the underlying neurobiology of mental disorders. Genes related to disease and abnormal brain growth and connectivity among brain regions have been reported.

Describing mental illness as a malfunction of the brain will help minimize the social stigmatization associated with them. Still, it is not possible to describe all mental illness in purely biological terms. Social and environmental factors are undoubtedly important. Mental representations, meaning and conditioning imply a whole level of processing that has to do with psychological abilities.

Figure 2. Major classes of mental disorder and their main symptoms. Mental illnesses display a high degree of comorbidity, in particular depression, and share many common symptoms, which are not restricted to perturbed mood.

Available medications are effective in treating specific symptoms for subsets of individuals affected by mental disorders. However, these treatments do not improve quality of life in a significant proportion of patients, including children and adolescents, and may show serious side effects. Pharmacotherapy is not the only option adopted for the prevention and control of mental illnesses. Maintaining psychological equilibrium fulfils important roles in the lives of many patients. Indeed, approaches other than pharmacotherapy are often preferred for the alleviation of low mood, anxiety and heightened stress-sensitivity. Similarly, inter-personal therapy, cognitive behaviour therapy (CBT), behavioural activation and related techniques are attracting increasing

attention for the control, prevention and treatment of mental disorders both alone and likely most effective in combination with pharmacotherapy (Figure 3).

Figure 3. Readouts in animal models of mental disorders and in the evaluation of drugs and other therapies.

6.2 Impact in basic science panorama and potential applications

Deciphering the biological bases of brain functioning and their association to emotion, thoughts and perception is essential for placing newly identified brain changes associated with mental disorders and treatment targets within a functional context. This requires the work of basic neuroscientists from different disciplines including cell, molecular and developmental biology as well as electrophysiology, brain circuits and behaviour.

It is necessary to move away from single-disease frameworks. Neurodegenerative diseases emerge as promising model systems for studying brain-behaviour relationships and the neural circuitry associated with psychopathology. Therefore, advance in the field would profit from the collaboration between basic scientists on neurodegenerative and mental disorders. The brain-only focus traditionally taken in research for these disorders should be extended to the study of brain-body connections. Basic research on the microbiome-gut-brain axis and on the brain effects of the immune response in peripheral tissues is particularly interesting.

Cross-interdisciplinary collaboration is essential for potential applications to come true. Basic researchers and clinicians (including neurologists, psychiatrists and psychologists) should join efforts. Beyond knowing that an intervention is efficacious, research initiatives are needed that clarify the mechanisms through which interventions work.

Together with neuroscientists and clinicians the contribution of researchers in human and social sciences is especially relevant in the context of mental disorders. There has been a historical confrontation between essentialist and non-essentialist perspectives to explain mental disorders. The first one stresses the biological nature while the second considers the cultural circumstance of the individual. Integrative approaches should overcome this debate.

6.3 Key Challenging Points

The complexity of mental disorders poses numerous challenges at the scientific, clinical and social levels. We identify three major challenging points:

6.3.1 Understanding the biological origin of mental disorders

Although remarkable advances have been made in the past few decades, we are still far from understanding how emotion, perception, cognition, executive function, motivation/reward and impulse control arise. This basic work is much needed to define which aspects of normal development, brain circuit structure or function are linked to the pathophysiology or to the emergence of behaviours that depart from a “normal” range. Among the urgent tasks to address the biological origin of mental disorders are: identifying genetic alterations; establishing the patterns and roles of epigenetic modifications; determining alterations in synapse function and brain circuit connections; defining the involvement of non-neuronal cell types such as astrocytes and microglia; and settling the influence of environmental factors that enhance or diminish predisposition to suffer mental disorders.

6.3.2. Bridging basic science progress to therapies

The progress in basic science discoveries has not yielded in parallel advances in the treatment of mental disorders. Indeed, most of the classes of drugs currently used to treat mental disorders were identified well before much of our current knowledge of brain biology was established (Spedding et al., 2005). In general, treatment planning in psychiatry depends on trial and error strategies. In view of the huge global burden of mental disorders and the inadequacy of current treatment, intensive efforts are needed to improve their management and prevention. Pharmacotherapy is likely to remain of central importance. In the research for better drugs, it is essential to clarify the mode of action of currently available drugs, and identify novel treatment targets and concepts. It is crucial to generate suitable animal models and to integrate the findings in these models, which are necessary to determine the therapeutic potential of novel pharmacotherapy, with human observations. Alternative therapies to pharmacology must be also developed. Examples as diverse as deep brain stimulation (DBS) and CBT are attracting serious attention as well as strategies based on cell and oligonucleotide therapies and genome and

epigenome editing. However, an efficient therapy may be harmful if a diagnostic is wrong. The difficult diagnosis for mental disorders prevents application of the right treatments and increases the risk of dangerous over-prescription. Diagnostic tools should be developed such as biomarkers for immune-inflammatory, synaptic and genetic and epigenetic alterations together with improved neuroimaging techniques.

6.3.3 Addressing the social impact of mental disorders

Mental disorders are often associated with social stigma and discrimination together with poor public assistance. Psychosocial approaches that empower the individual suffering a mental disorder and promote community awareness and support are necessary. Analysis of welfare policies on mental health along history in different countries should illuminate the way ahead in this regard.

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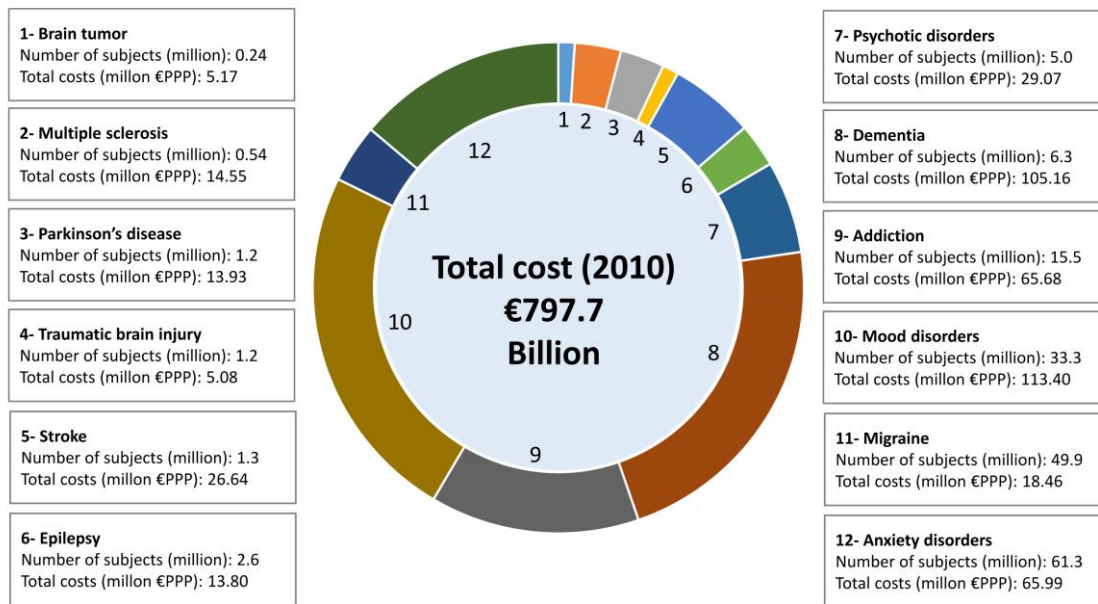


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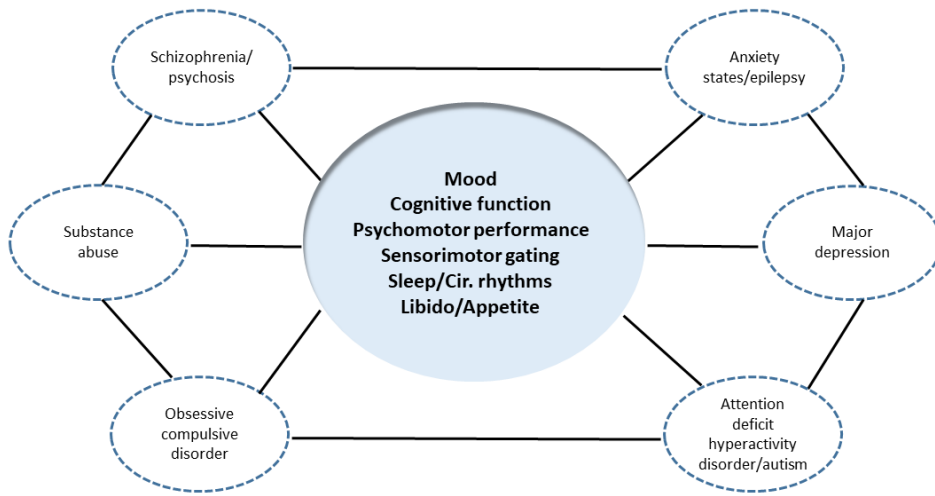


Figure 2. Major classes of mental disorder and their main symptoms. Mental illnesses display a high degree of comorbidity, in particular depression, and share many common symptoms, which are not restricted to perturbed mood.

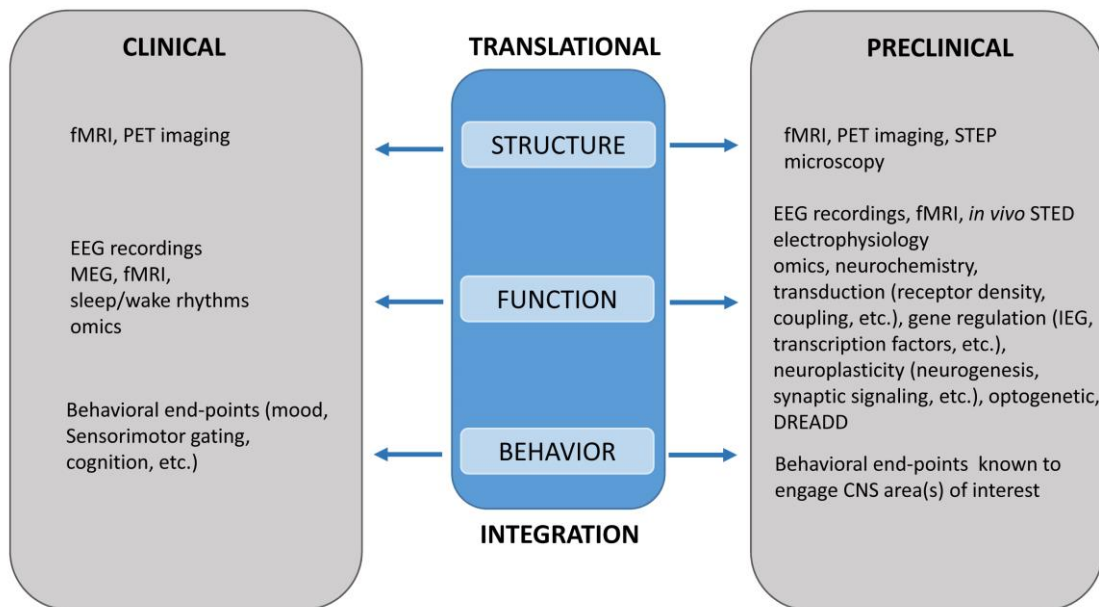


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