BRAIN, MIND & BEHAVIOUR

Topic Coordinators
Eloísa Herrera (IN) and José Antonio Esteban (CBM)

EXECUTIVE SUMMARY

The brain is arguably the most complex biological system in the known universe. The substrate of our thoughts, the way we built our societies through complex languages and the impressive cultural and technological advances at our disposal, have been all developed thanks to the activity of our brains. The next few decades are going to be strongly influenced by our capacity to integrate different levels of complexity to understand how neural circuits produce thoughts and behaviors. However, we are still far from achieving this goal. Understanding the development of the brain and its inner workings is already a formidable task. Even minor alterations of brain function may be responsible for mental disorders that have devastating impact for individuals and communities and are a leading cause of disability in developed countries. In addition, the nervous system is notoriously reluctant to repair itself after damage, which places a great burden on millions of people living with motor or sensory disabilities. Despite significant advances in recent years in the treatment of brain disorders, they are still considered a critical unmet health problem in Spain and Europe. This is due to the poor knowledge of their aetiology, the complexity and variability of symptoms, the demanding diagnosis, the limited therapies and public care as well as the social stigma they often pose. The incorporation of genetics, molecular and cellular biology to the study of the nervous system has greatly accelerated our understanding of some of these problems. However, we need to develop more sophisticated techniques of monitoring and modifying brain function as well as better theoretical frameworks in which the valuable pieces of information that we collect are transformed in biological understanding. It is imperative that the CSIC participates on this revolution, as the risk of lagging behind may have long-term consequences. The CSIC counts with excellent biologists, chemists, mathematicians, physicists, engineers and outstanding experts in humanities and social sciences. Basic neuroscience researchers aim at understanding how the brain elaborates emotions, thoughts and behavior 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 in this context aim at understanding the role of the various cognitive functions in the emergence of dynamic societies and civilizations. Approaching the study of brain function and mental disorders from different but complementary perspectives and research expertise is a critical strategy to achieve important breakthroughs in neurosciences in the upcoming years.

Introduction

The brain specifies and controls every aspect of our life, including rational thinking, emotions, heart-beat, breathing, food and liquid intake, sleep and sexual desire. Therefore, a high quality of life and well-being require that our brain stays healthy and properly operative. Disorders that are the consequence of brain dysfunction, such as depression, Alzheimer's disease, dementia, schizophrenia, migraine, sleep disorders, Parkinson's disease, pain syndromes, addiction, etc, have turned into a major health problem worldwide costing as much as cancer and heart diseases together. Brain disorders are currently estimated by health economists to account for 45% of Europe's annual health budget. In fact, the economic cost of brain disorders in Europe is estimated to be ca. € 800 billion per year and patients suffer a significant loss of quality of life during the course of the disease, which also impacts strongly on their families and their social network. With an increasingly aging population in Europe, the prevalence of the most common neurological and psychiatric disorders is expected to grow dramatically and it is imperative to find truly effective approaches that reduce this huge society problem, including the impact on care-givers and the resultant loss of productivity, employment and massive economic burden. Therefore, urgent solutions that prevent, diagnose, palliate or treat neurological diseases are needed.

The complexity of connectivity between neural cells in the brain is mind-boggling. The human brain contains eighty-six thousand million neurons and many more glial cells. Each neuron can contact with thousands or even tens of thousands of others. Our brains form millions of new connections for every second of our lives. Furthermore, the pattern and strength of these connections is constantly changing and no two brains are the same. It is in this changing connectivity that memories are stored, habits learned and personalities shaped, reflected in reinforcing certain patterns of brain activity, and losing others. Therefore, finding out what is wrong in each particular brain disorder is extremely complicated and, as a consequence, diagnosing and treating brain diseases will require much more effort compared to other diseases. Brain research should continue at the most basic level to provide the bricks with which to build a comprehensive model of brain function and dysfunction. We believe that the best way to fight brain diseases is to solve the fundamental questions about brain development and function and to use these ideas to understand the mechanisms of brain dysfunction. We must intensify the scientific effort to understand normal and abnormal behavior emanating from impaired brain function and spanning molecular, cellular and network mechanisms to social and environmental determinants. Understanding the brain provides valuable knowledge (critical in a knowledge economy) that has the potential not only to treat disease, but also to innovate in the areas of artificial intelligence, brain-machine interface, robotics and new technology. The commitment of funding agencies to basic research in neuroscience has advanced our understanding of some of the mechanisms governing brain function in recent years, and recent methodological breakthroughs now offer a powerful opportunity to ease the societal burden of brain disorders and innovate at the frontiers of technology.

As the most important research institution in our country, the CSIC has the responsibility of contributing significantly to the knowledge of nervous system biology in both health and pathological conditions. Over the past decades, our institution has incorporated competitive lines of research on different neuroscience areas. We have identified eight specific challenges in brain research that are closely interconnected and to which the CSIC could contribute greatly because it has a significant number of excellent specialists capable of addressing them competently.

The first five challenges focus on fundamental mechanisms of how the nervous system develops and functions. The CSIC has a substantial number of excellent groups with the potential to contribute significantly to understanding **how neural networks emerge (challenge 1)** during embryonic stages and late postnatal periods to establish a correct connectivity and how the different brain components integrate at different biological levels from **genes and circuits to orchestrate complex behaviours (challenge 2)**. The knowledge generated by basic scientists using simple model organisms combined with novel brain imaging techniques, large-scale computational analysis and machine-learning approaches will help to discover how the brain solves complex problems, such as managing emotional states, understanding languages, etc. Further diving into these issues will lead us towards higher emergent properties of the brain, such as **cognition, collective behaviour and consciousness (challenge 3)**. These investigations, in turn, should deliver innovative technologies that will impact on many areas of society, including ethics, philosophy or laws and legislation. For instance, in the search for a more egalitarian society, it will be essential to understand the influence of nurture vs nature in establishing stereotypic behaviors such as gender bias, both at the biological and social level. **The study of the neurobiology of sex and gender (challenge 4)** is as relevant as it is controversial, and one of the main challenges in this regard is to take into account the intrinsic biological diversities of females and males and, at the same time, not to feed the culture of gender dichotomy that is often articulated by society and its hierarchies through gender bias.

It has become increasingly evident that bidirectional communication between the nervous system and peripheral organs has an important effect on our mood and behaviors as well as on the pathogenesis of many brain disorders. This is approached by **challenge 5, body-brain microbiome interactions**. Therefore, it will be determinant in the next few decades to unveil the role of the immune system, metabolic processes, gut-brain axis and microbiome in regulating brain activity.

The following three challenges will make it possible to identify measures to help alleviate the burden of brain pathologies in our increasingly aging European society in order to maintain healthy individuals with functional cognitive abilities in old age. The challenges in this block should provide solutions **to diagnose and treat mental disorders as well as to advise on their social acceptance (challenge 6)**. Indeed, mental disorders have a devastating and growing impact on our societies and CSIC researchers should face the challenge of determining the biological and social causes and consequences of these disorders, and finding efficient therapies. It will also be essential to find ways to maintain the best possible cognitive performance as we age and to guide society in caring for patients affected by **neurodegenerative diseases and other age-related brain conditions (challenge 7)**. Neurobiologists, mathematicians, informaticians, engineers, experts in robotics and nanosciences should then cooperate and capitalize on the new knowledge generated by basic researchers to devise methods to **improve brain regeneration and functional recovery after brain and spinal cord damage (challenge 8).** Injuries to the brain and spinal cord are amongst the leading causes of death and long-term disability in young people. Instruments of regenerative medicine such nanospheres, liposomes and mesoporous nanostructures or stem cell-based therapies, together with the stimulation of deep brain structures using nanotechnology strategies and new-generation activatable chemicals are emerging as future prospects for the treatment and diagnosis of acute brain damage and will be explored for further application. Finally, rehabilitation of patients with central nervous system (CNS) injuries driven by advances in novel robotics designs is now a powerful strategy for restoring disabilities, particularly in relation of motor functions, and will be also exploited.

Common actions to implement

To tackle these large-scale challenges and make breakthrough advances keeping our institution at the cutting-edge of nervous system research in Europe and the rest of the world, the CSIC should embrace ambitious steps towards implementing the following common strategic measures that are further detailed on the different challenges:

1. To increase the investment in centers of excellence and teams working on brain research. Spain is regarded as having a long tradition in neuroscience research, which not only should be maintained, but strengthened in order to improve the visibility of the country and the CSIC in the world. CSIC has two main centers that have played a fundamental role for development of neuroscience research in Spain: The Cajal Institute (IC) and the Neurosciences Institute (IN), the latter being a “Severo Ochoa” Center of Excellence for the last 6 years. In addition to these two medium-scale monographic institutes, neuroscience research in Spain is generally carried out by small teams distributed in university departments, hospitals and biomedical research institutes (e.g. CBM). Spanish neuroscience has acquired a privileged position nationally and internationally in recent decades. The CSIC should take advantage of this situation to expand and strengthen brain research in Spain, and should make strategic progress in organizing and promoting excellence neuroscience centers that should concentrate critical mass and infrastructure needed for frontier investigations in this field. A pan-national network of virtual nodes would also help to enhance the international competitiveness of the CSIC-neuroscience. Research centers such as the IC, the IN, IEGD (Institute of Economics, Geography and Demography) or CAR (Centre for Automation and Robotics) have demonstrated that thematic institutes are an excellent way to nurture competitive science and therefore it would be crucial to maintain and reinforce this strategy. Nevertheless, it is important that other competitive brain research teams spread across CSIC's multidisciplinary centers are also supported and empowered as a complementary strategy to maintain diversity and exchange of ideas with researchers from other fields.

2. To foster interactions among different teams and centers. The inherent complexity of the nervous system has led us to realize that a higher level of integration of different biological areas and other disciplines is now essential to make significant progress in brain research. To obtain revolutionary and transformative results, as well as to maximize our translational impact, CSIC groups working on different aspects of neurobiology should move beyond their particular areas of expertise and embrace initiatives that reinforce and intensify contacts with clinicians, engineers, informaticians and social science investigators. Particularly, productive interactions with investigators in the health system will be critical to crystalize the translational potential of our investigations in brain disease. Actions to promote collaborative work among the CSIC groups and centers will certainly increase our productivity and raise the international competitiveness and visibility of our institution.

3. To launch technological infrastructures and platforms at the institutional scale. We are living a revolution in neuroscience thanks to the recent flourishing of technological developments that allow us to investigate questions that were unreachable only few years ago. However, technology keeps moving forward very rapidly and core facilities and platforms, such as imaging facilities or genomic platforms need to be continuously renewed with state-of-the-art equipment and be staffed with highly specialized personnel. Otherwise, the maintenance of competitiveness is unreachable. Many of the today's major challenges in relation to the development and dynamics of functional neural circuits arise as a natural consequence of the in-depth and detailed, but as yet unimplemented, knowledge provided by new technologies. Dispersion of platforms and common services for the generation of animal models, next generation sequencing, drug screening, big data analysis or neuroimaging should be avoided. Instead, common services working already in the different

CSIC centers should be strengthened, better funded and staffed with highly qualified technicians. Reinforcing and disseminating the already existing services would avoid redundancy in different CSIC centers and reduce costs.

4. To train and recruit researchers at the frontier of different disciplines. Understanding the brain will require not only to organize and share big-datasets in user-friendly repositories, but also to educate the younger generations into profiting of these data. We need investigators that can navigate comfortably between physics, biology and information theory. The elaboration of novel hypotheses that can comprehensively describe the complexity of the circuit development and functionality requires out-of-the-box thinking, the use of big-data languages to encode biological meaningful analysis, and also informed biological perspectives. This effort is going to require a true interdisciplinary approach between neurobiologists, physicists and biocomputational researchers. The CSIC should implement two main actions to accomplish this demanding challenge. First, by taking advantage of the large number of CSIC investigators working on distant disciplines, it should launch an intramural fellowship program for PhD students and young postdocts devoted to favor their training in a cross-disciplinary manner. Second, it should make an important effort in recruiting researchers with highly interdisciplinary profiles that serve as bridge between basic and clinical neuroscience or fill the existing gap among neurobiology, informatics, robotics and social sciences. The CSIC's recruiting policy should make a great effort to attract these type of exceptional professionals. This may require novel and more dynamic recruitment approaches to attract talent in a fast-paced and global environment, overcoming the constraints and rigidities of our 80-year old institution that often result in a loss of opportunities.