Editorial

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The future of clinical neurosciences: View from the bedside

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Medicine has made immense progress, largely due to the fact that it is now firmly anchored in an ongoing science base. With this in mind, how should we organize the future of clinical neuroscience from a practical point of view, namely how to test new treatments and how to decipher the pathophysiology of neuropsychiatric disorders in patients? If we want our discipline to become the most advanced in medicine, we need to solve two important questions: How to scientifically examine our patients in order to make real discoveries, and not simply to reproduce descriptive studies? What are the best educational programmes to be implemented in order to provide an optimal medical and scientific training to our students?

A large number of illnesses of the nervous system can now be cured. In tomorrow's world, we must be ready for several upheavals: the four 'Ps'. (1) Medicine becomes *Predictive*. In these 'patients without symptoms', a disease will be detected before it is expressed with the help of various clinical and biological markers. (2) Treatments will be *Personalized* with the major pathological scourges, including stroke, neurodegenerative diseases and so on seen in the form of diverse underlying causes and mechanisms of action that will dictate a movement towards 'one patient – one treatment'. (3) Medicine will become *Preventive*. Many disabling conditions will be cured with personalized treatment before the appearance of any symptoms ('a treatment without symptoms'). (4) Medicine will become *Participative*. The patients themselves will take part in the implementation of their treatment, a sort of 'medicine without a doctor'.

Keeping this in mind, is it not the time to move forward, all the more since we start to understand how the brain functions and how it dysfunctions. But why has there been such a delay in comparison to other disciplines? The answer is simply because the brain possesses a complexity that defies imagination – a sort of small-scale version of the complexity of the universe. What has led to this leap in our understanding of brain function have been major advances in neuroimaging, neurogenetics, neurophysiology and neural modelling and clinical semiology.

Apart from positron emission tomography, we are essentially talking about magnetic resonance imaging (MRI). These scanners have already transformed neurological and psychiatric practice by enabling the location and even identification of tumours, brain ischaemia, multiple sclerosis, neurodegenerative disorders and so on. However, the MRI technique remains a crude localization method when we remember that the brain comprises 85 billion neurons and that each neuron has tens of thousands of connections with its neighbours and it generates nearly a billion of billions of signals per second! It remains to be understood how these neurons communicate with each other. This is the goal of emerging technologies in physiology and cellular imagery including optogenetics. In brief, neuroimaging in patients does not mean much without experimental physiology.

Neurogenetics is obviously at the forefront of attempts to an understanding of the principle causes of neuropsychiatric disorders, because we now have the ability to decode the entire human genome. This is the case for numerous hereditary diseases, for which relatively homogenous clinical profiles may be the result of numerous mutations within a large number of genes. What can we expect for the most frequent and multifactorial diseases such as schizophrenia, epilepsy, multiple sclerosis, Alzheimer and Parkinson diseases? The answer lies within epidemiological and epigenetic research, which enable us to tease out the relative contributions of genetics and environment. Let us hope that the power of new molecular biological

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techniques (such as Crisp-Cas9) will enable us one day to bridge the gap that exists between the causes of these disorders and their clinical expression. An example showing the strength of a synergistic bench and bedside approach.

The latest neurophysiological techniques now enable us to understand the function and dysfunction of major neural pathways in an increasing number of pathologies. However, even though we know how one neuron communicates with its neighbour, we still do not understand how a given signal is selectively transmitted within a neural network. Perhaps because we tend to forget that the other half of the brain is composed of glial cells! If, at the bed of patients, we want to evaluate new drugs to cure conditions such as neurodegenerative disorders, we will have to conceive ligands, which simultaneously target neural and glial cells. A good clinical investigator needs to be an experienced pharmacologist.

Neural modelling and systems analysis allow the interpretation of an increasing amount of health-related data. These rapidly expanding disciplines are enabling us to understand the physiological organization of neural structures at a system level and to understand better the flow of information within brain circuitry. Perhaps even more important is the rapid development of a digital medicine, brain–machine interface and robots. The power of computing sciences has reached such a level that some optimists are beginning to suggest that we will soon understand how our physical brain produces thought and consciousness, which until we can prove otherwise could still be considered non-physical. There is no doubt that the clinical scientist of the future should get a robust training in neuroinformatics.

Finally, and this is my own experience at the Salpêtrière hospital, these recent and promising methodological developments do not mean much if not documented by a strong semiological approach. Isn't it the best way to analyse the intellectual, emotional and motor behaviours in patients compared to controls? To listen and to observe our patients is indeed of crucial importance to provide an exquisite clinical research, that is, to avoid the publication of articles of mediocre quality.

It is therefore important that the training of young neurologists and psychiatrists must include more than ever the coming technological developments and thus interdisciplinary research, which is at its foundation. Whether a medical student wishes to specialize in neurodegenerative diseases or epilepsy, in multiple sclerosis or movement disorders, in schizophrenia or depression, they will need a full and appropriate medical and scientific training. In my experience, the best way is to train teams of 'doctor–researchers' (who will carry out research 'at the bed') and 'researcher–doctors' (who, with a good medical training, work 'at the bench'). These two categories of investigators will therefore be able to understand each other's approaches in such a way as to create bridges between clinical and research practice to the ever-greater benefit of patients.

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